

University of Dundee

## A Continuous Flow Strategy for the Facile Synthesis and Elaboration of Semi-Saturated Heterobicyclic Fragments

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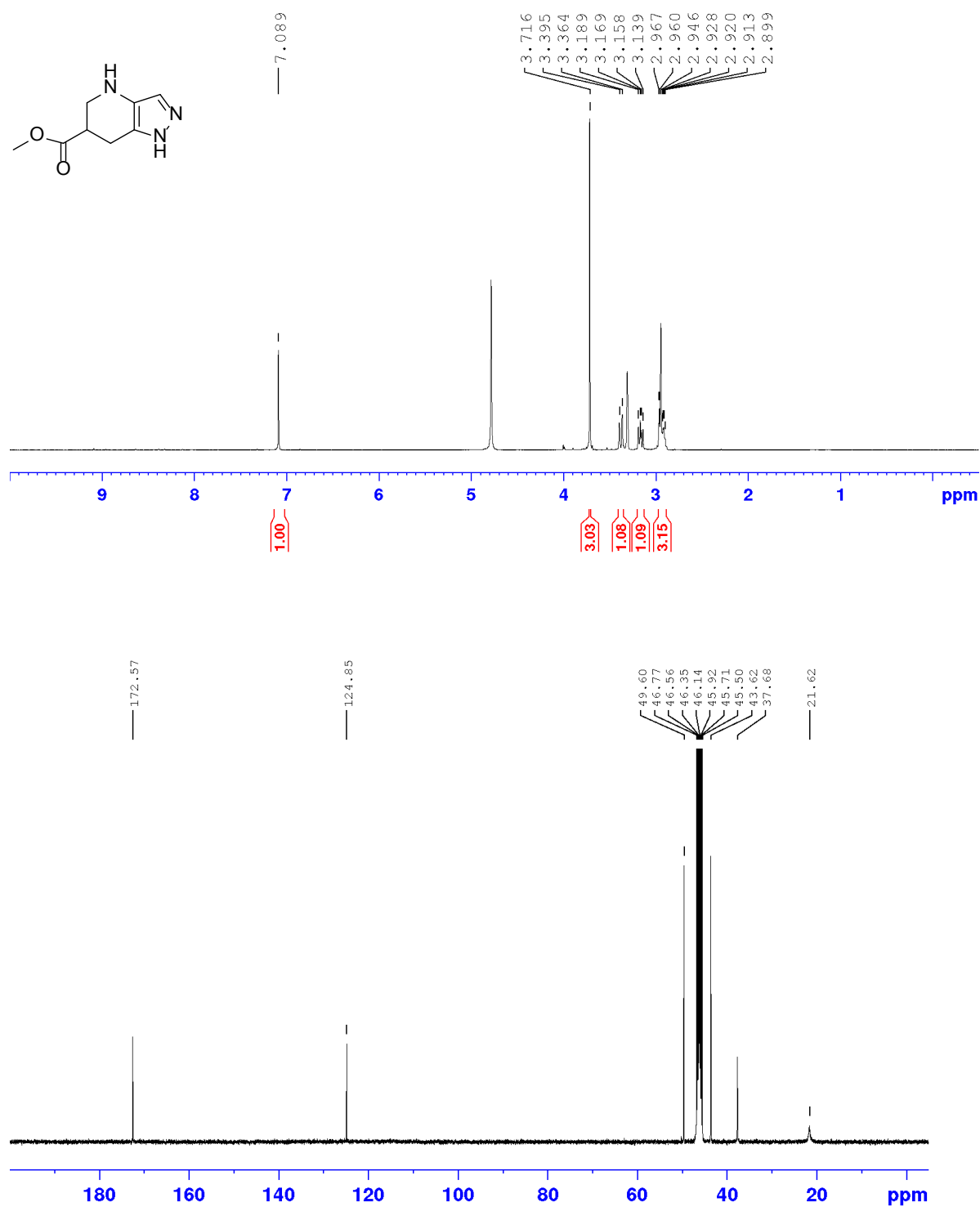
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## 1. Fragment criteria of the Drug Discovery Unit (DDU)'s fragment library

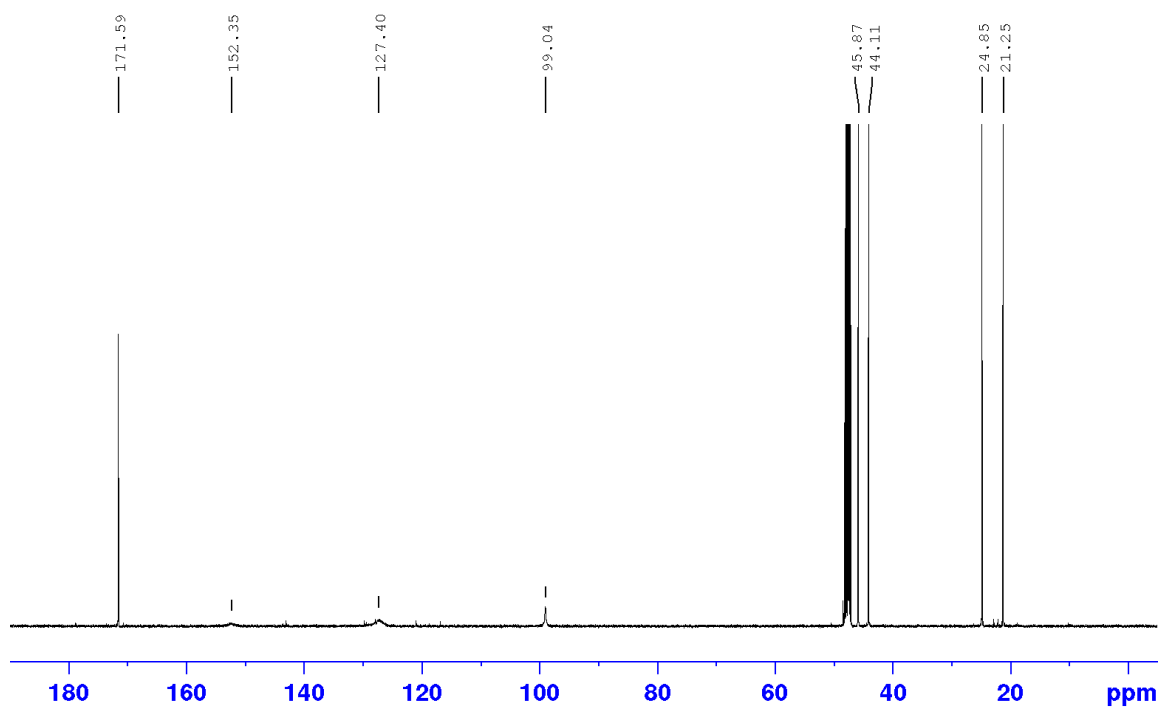
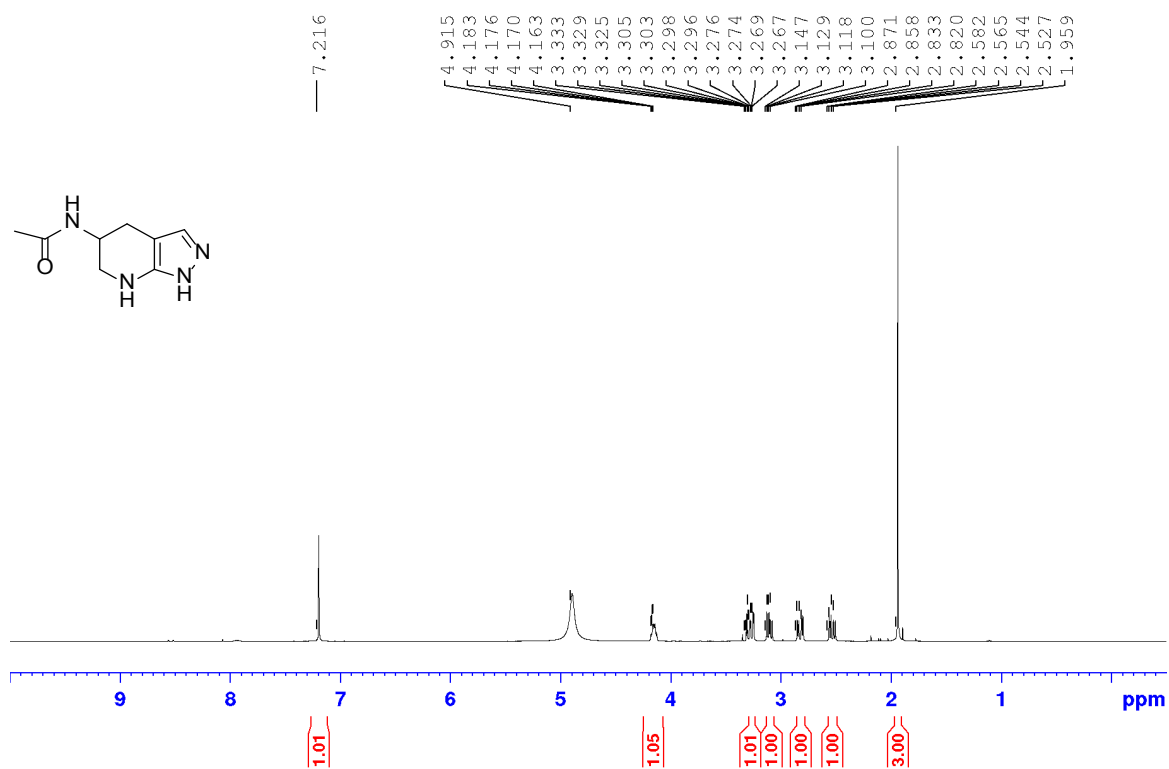
| Fragment criteria <sup>a</sup>  |   | DDU range |
|---|---|-----------|
| LogP  |   | -2 to 2   |
| LogD  |   | -2 to 2   |
| Heavy atom count  |   | 5 to 18   |
| Hydrogen bond acceptor  |   | ≤ 6       |
| Hydrogen bond donor   |   | ≤ 3       |
| Total polar surface area  |   | ≤ 90      |
| Rotable bonds   |   | ≤ 3       |
| Solubility  | Sample concentration > 1 mM based on comparison to residual DMSO-d <sub>6</sub> peak. |           |
| Stability   | < 1% increase in impurities after 48 hours  |           |
| Aggregation   | No evidence in the waterLOGSY of aggregation of the compound in buffer.               |           |
| Purity  |   | ≥ 95%     |
| [a] Physicochemical and quality control parameters employed by the DDU. |   |           |

## 2. NMR spectra

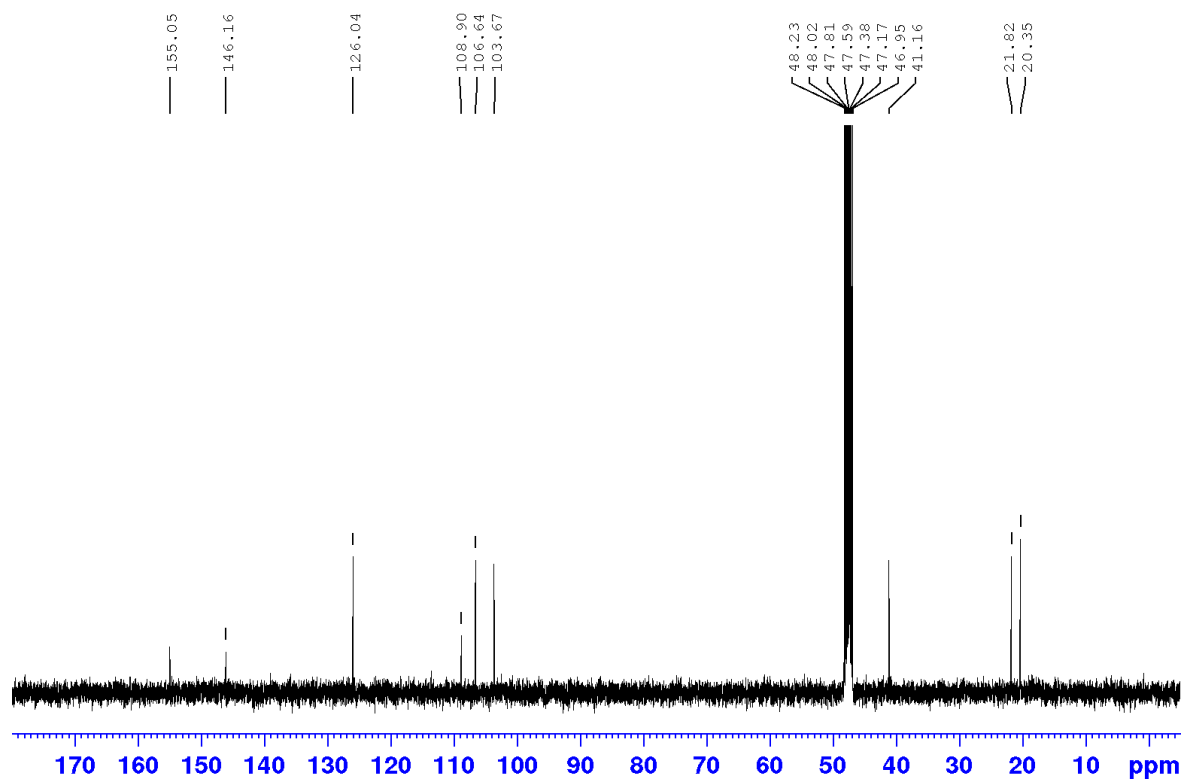
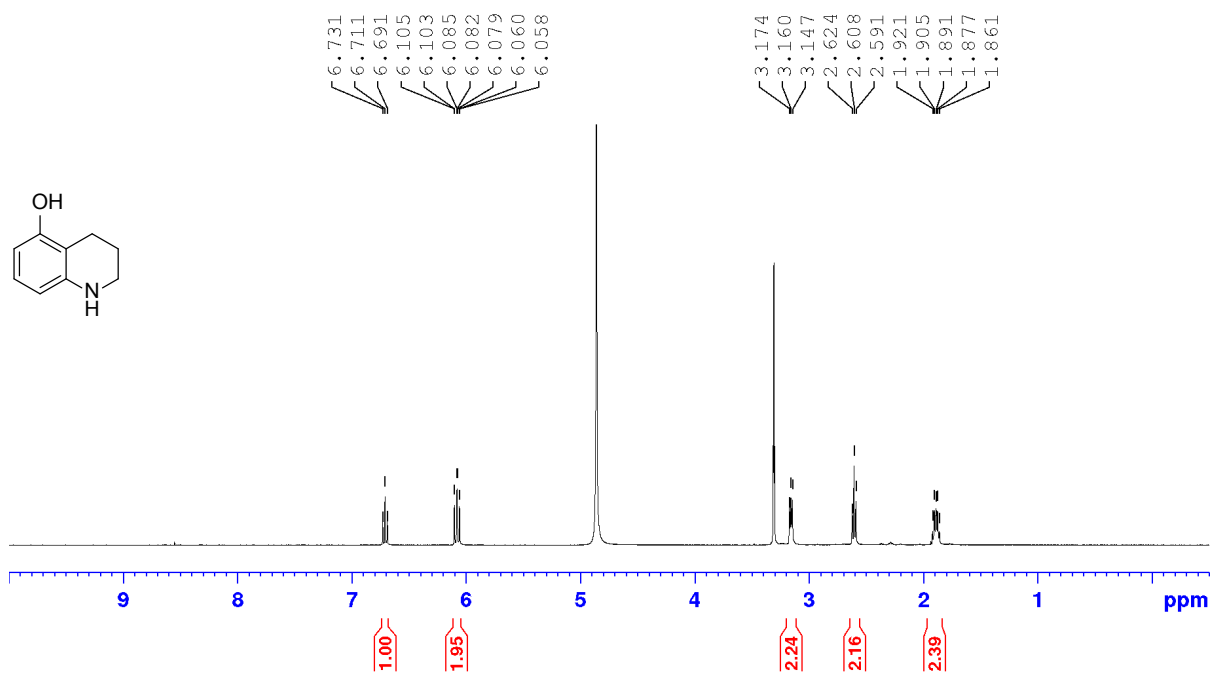
methyl 4,5,6,7-tetrahydro-1H-pyrazolo[4,3-b]pyridine-6-carboxylate (**18**)



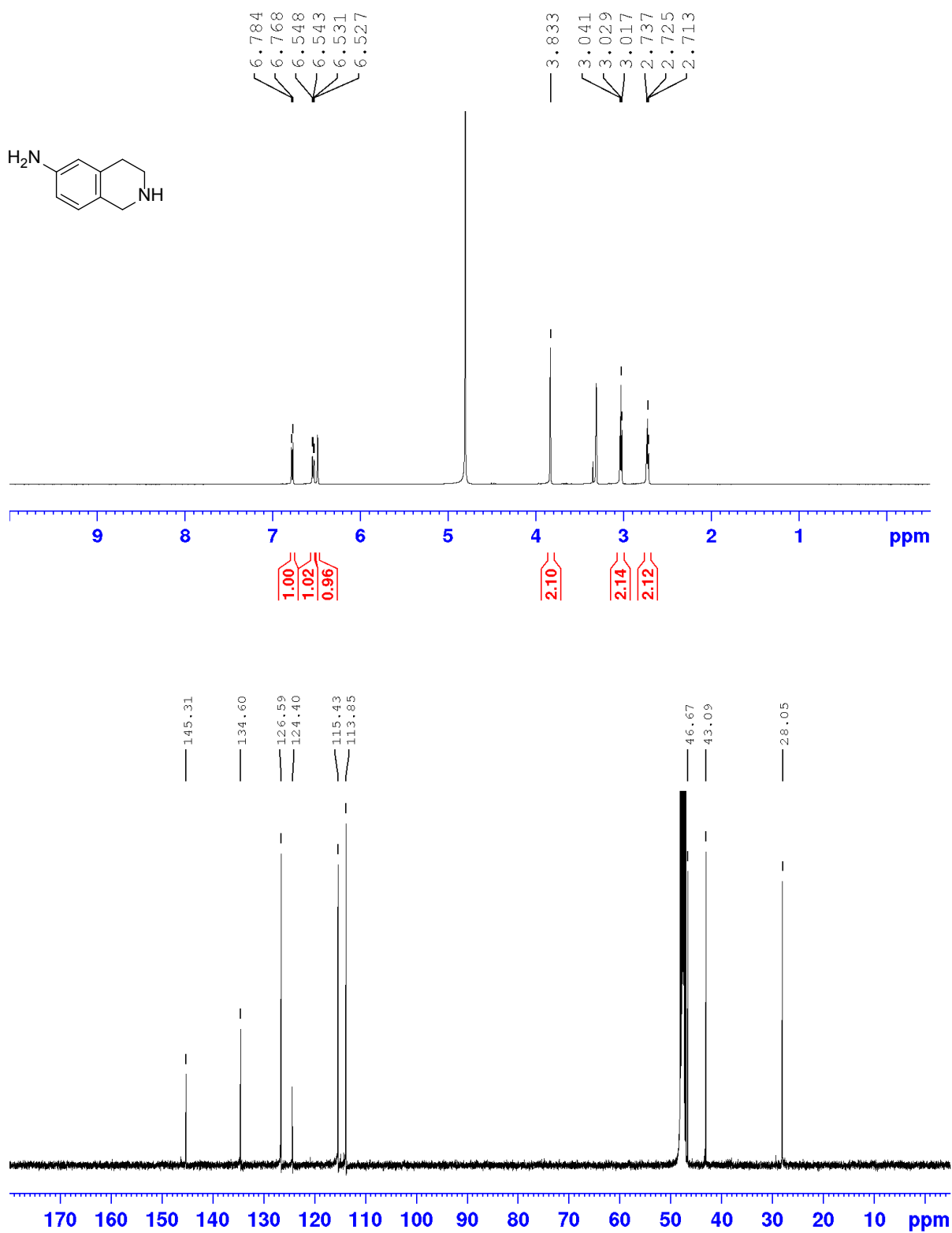
N-(4,5,6,7-tetrahydro-1H-pyrazolo[3,4-b]pyridin-5-yl)acetamide (**19**)



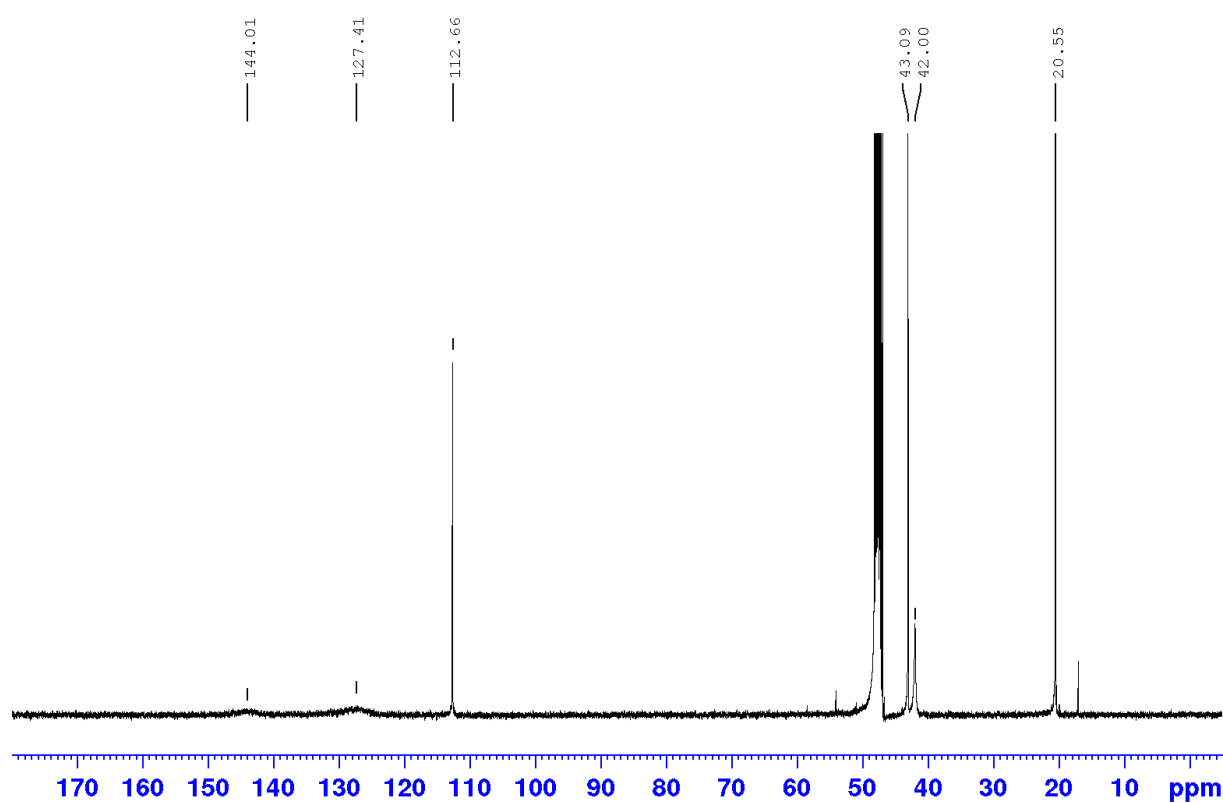
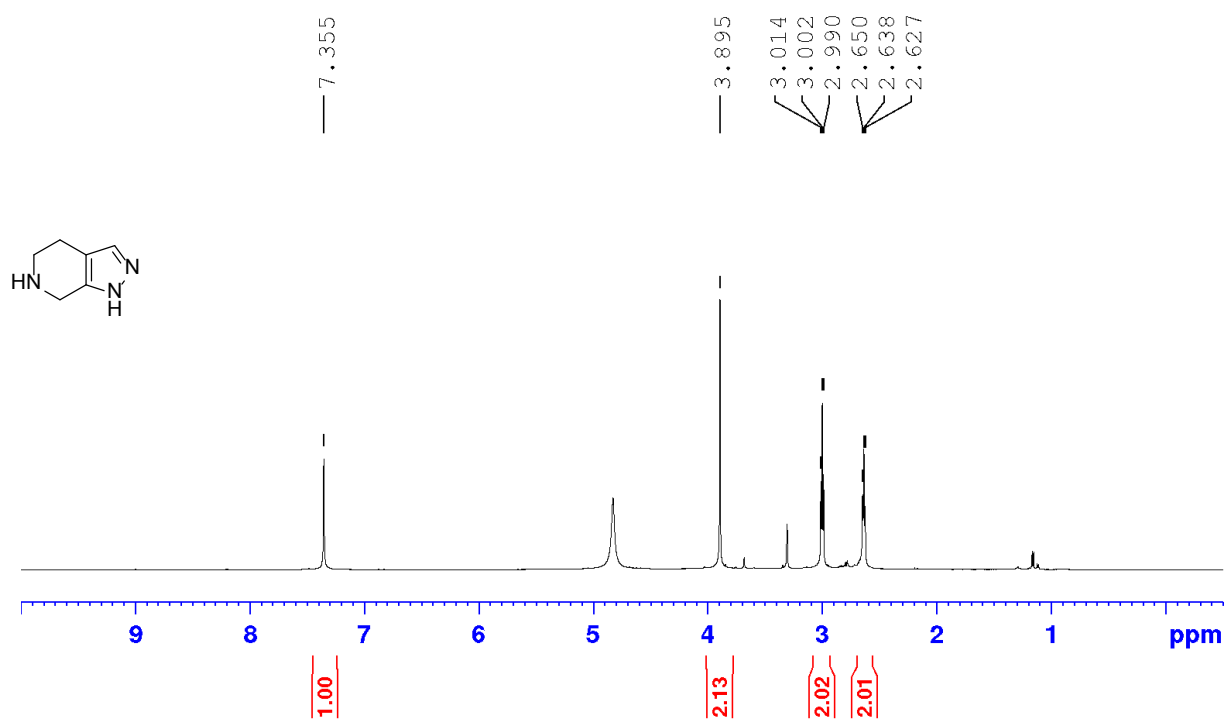
1,2,3,4-tetrahydroquinolin-5-ol (**20**)<sup>1</sup>



1,2,3,4-tetrahydroisoquinolin-6-amine (**21**)<sup>2</sup>

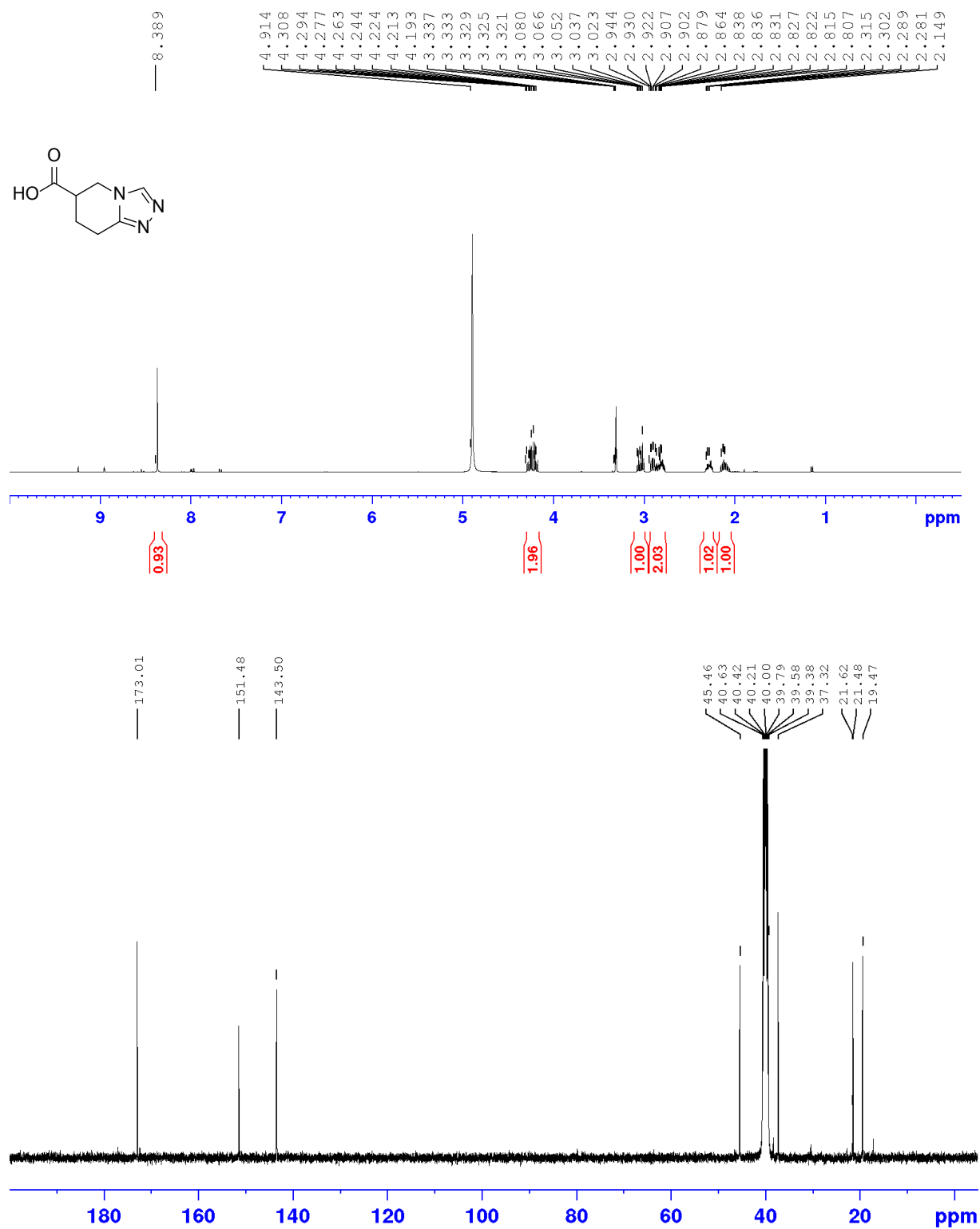


4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine (**22**)<sup>3</sup>

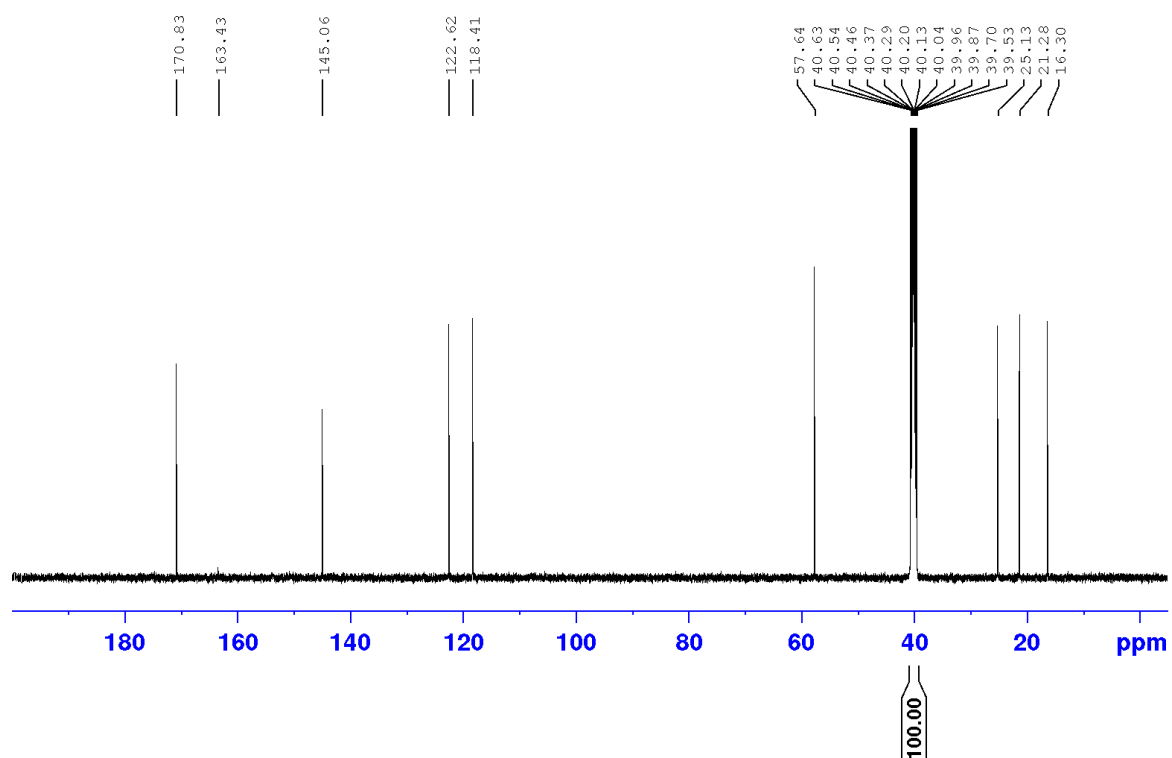
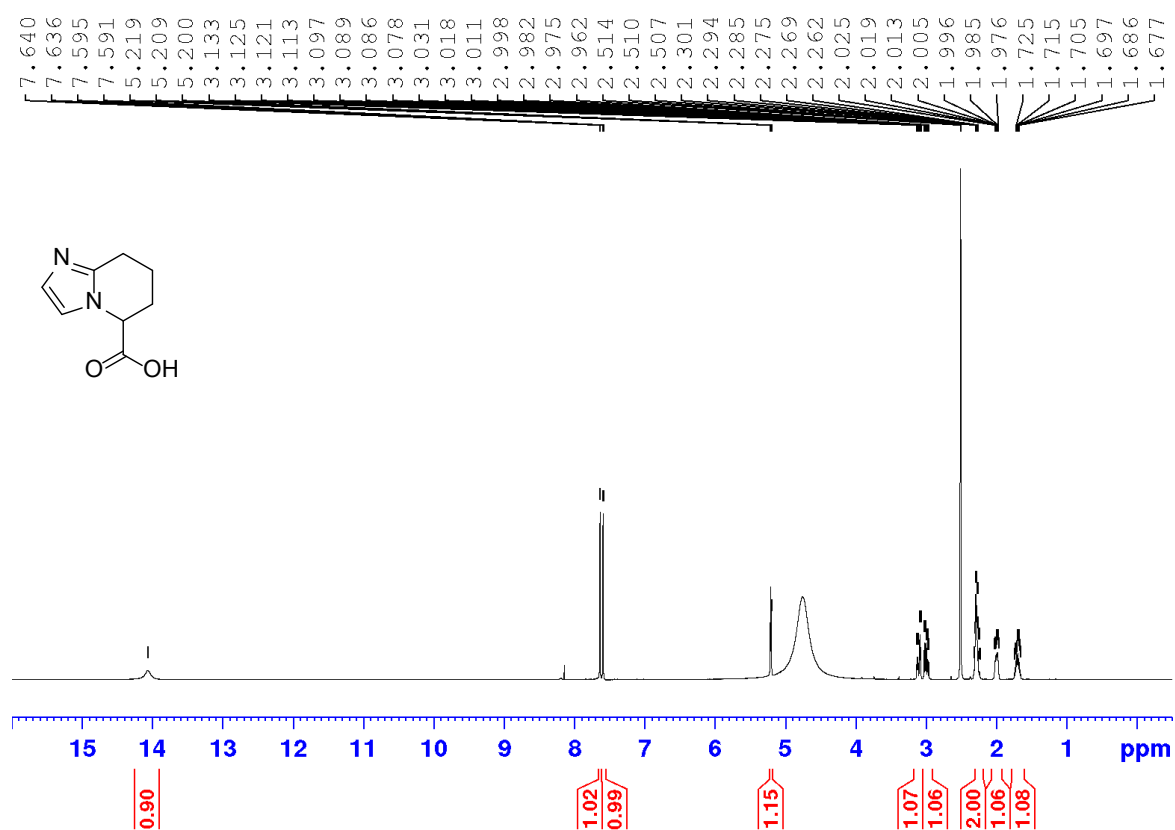




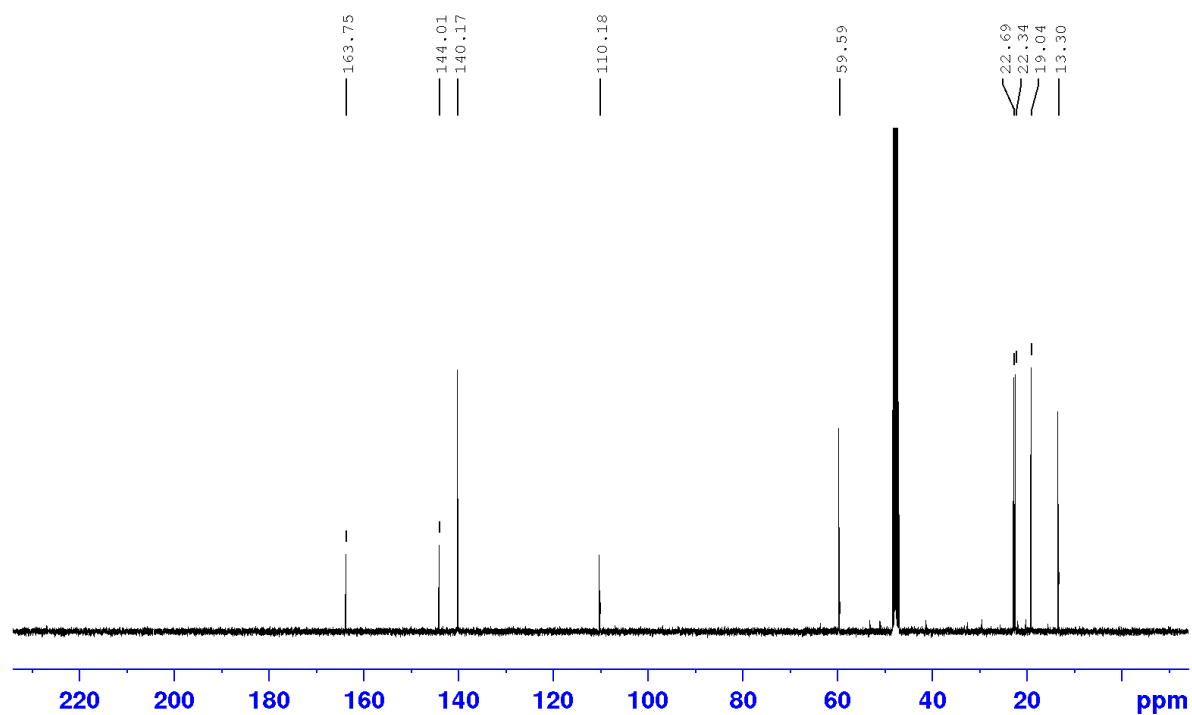
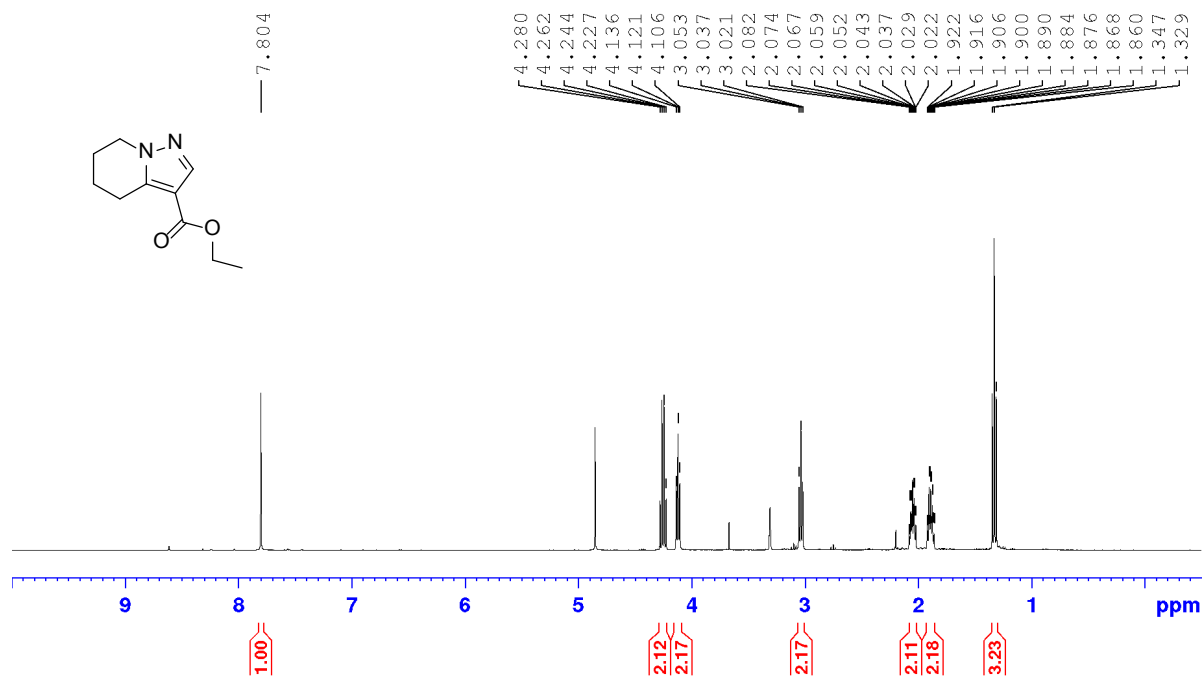
5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylic acid (**23**)<sup>4</sup>



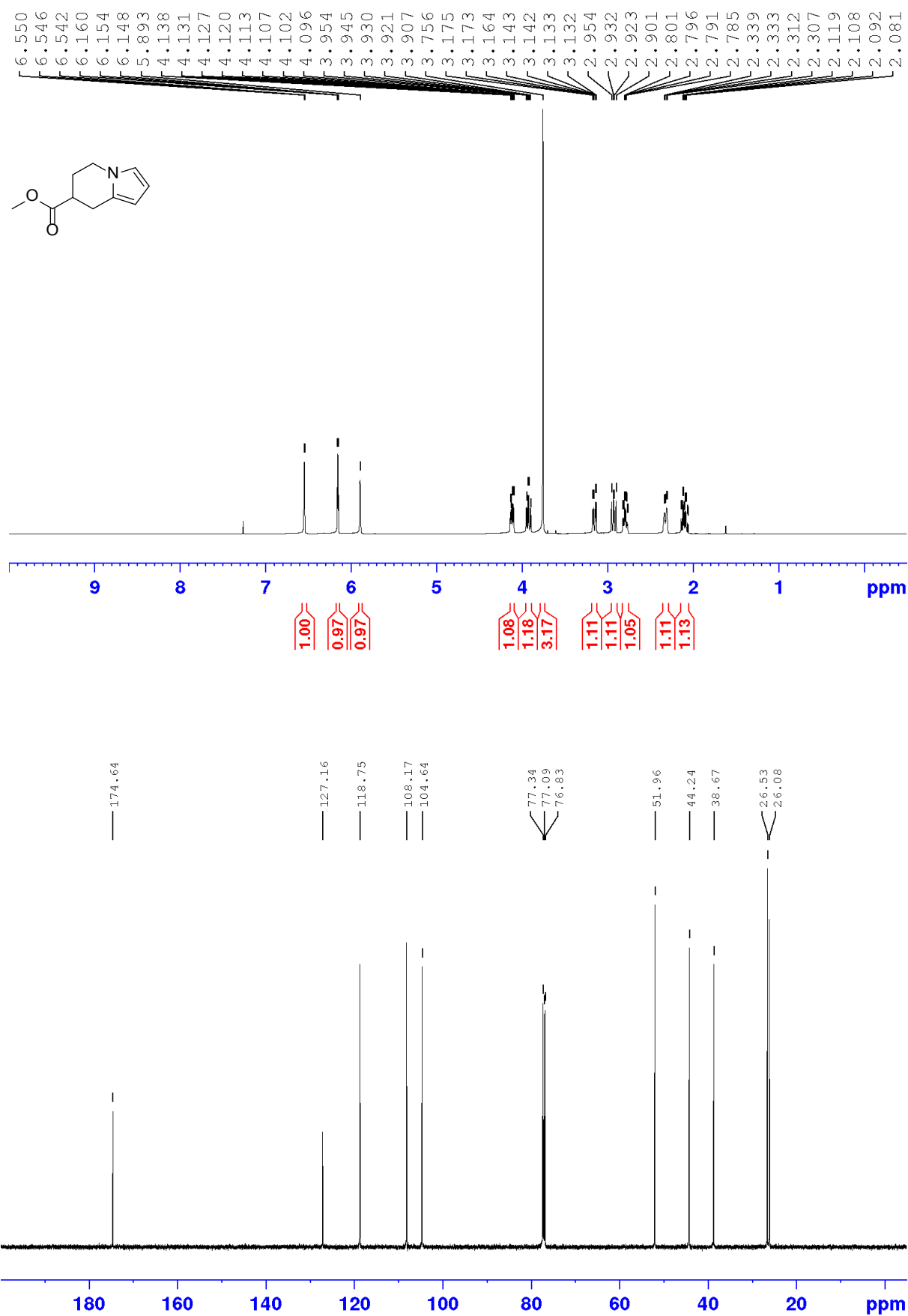
5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-5-carboxylic acid (**24**)<sup>5</sup>



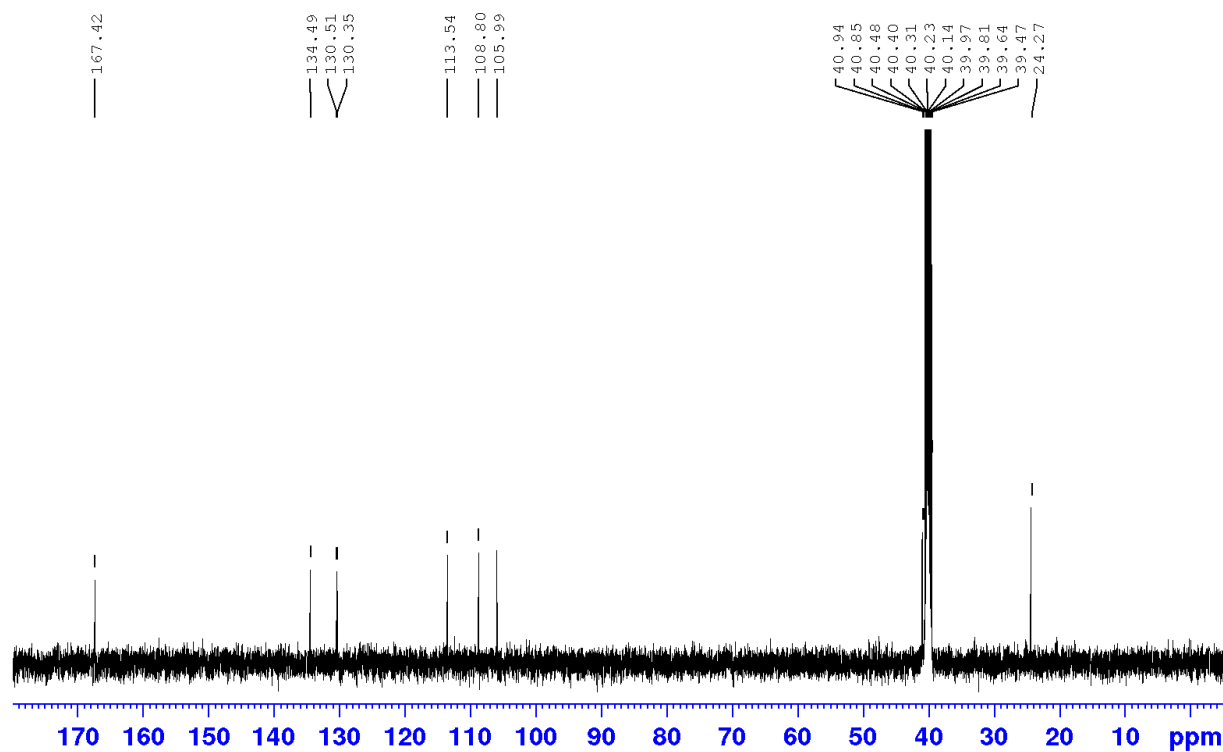
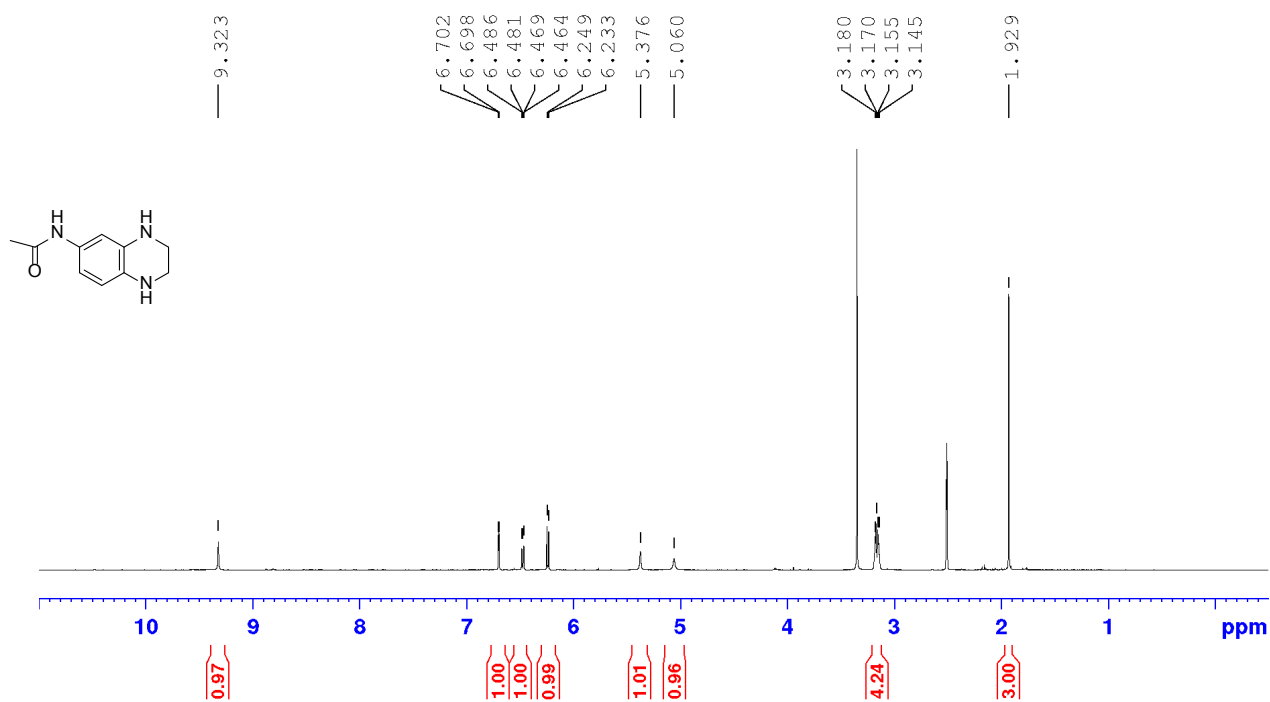
ethyl 4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-3-carboxylate (**25**)<sup>6</sup>



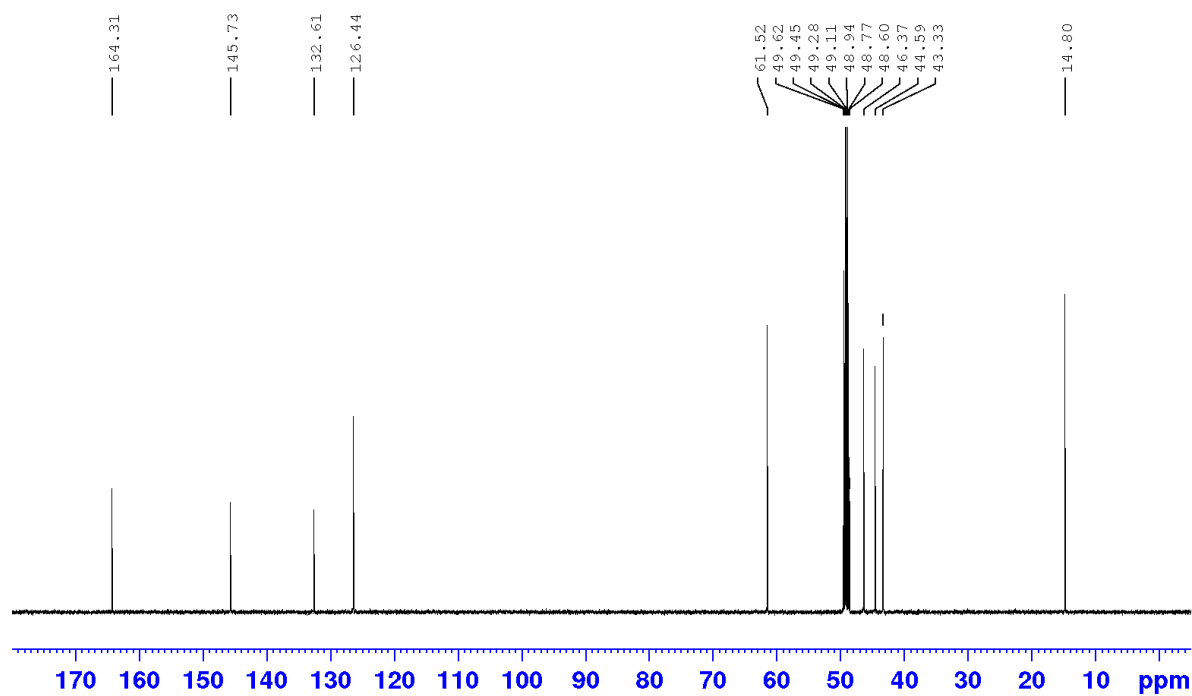
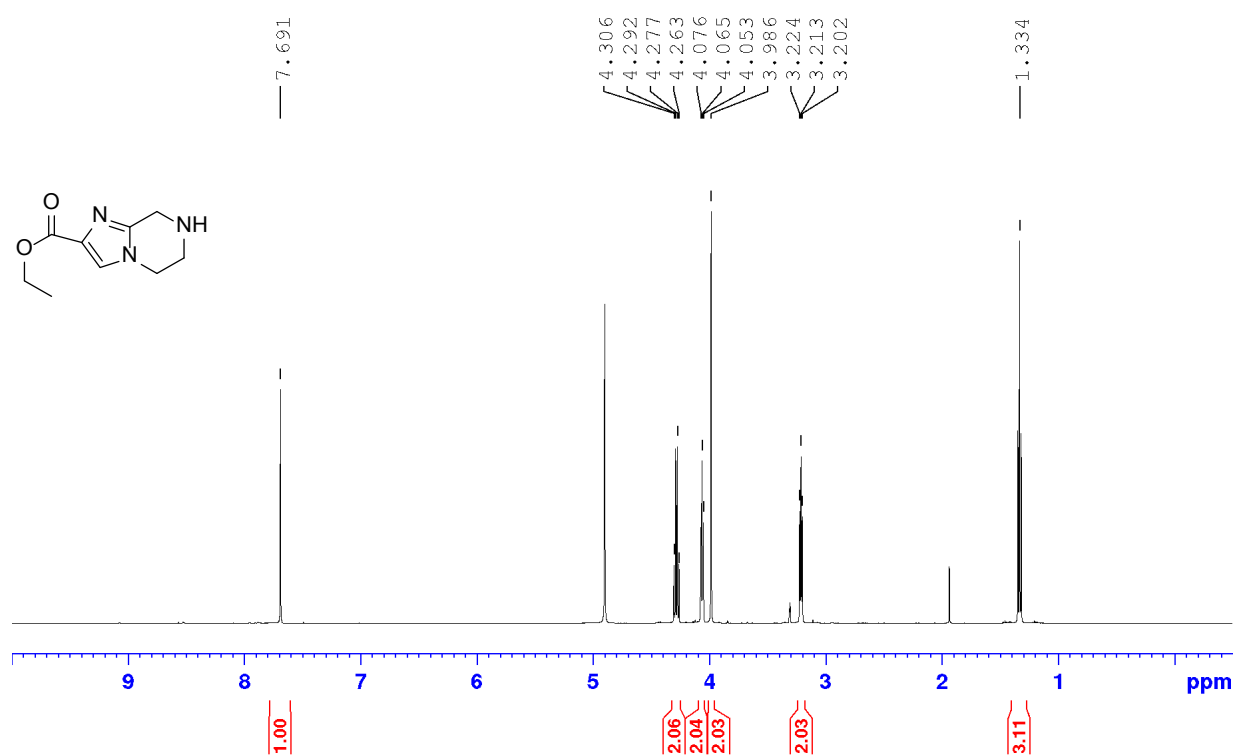
methyl 5,6,7,8-tetrahydroindolizine-7-carboxylate (**26**)



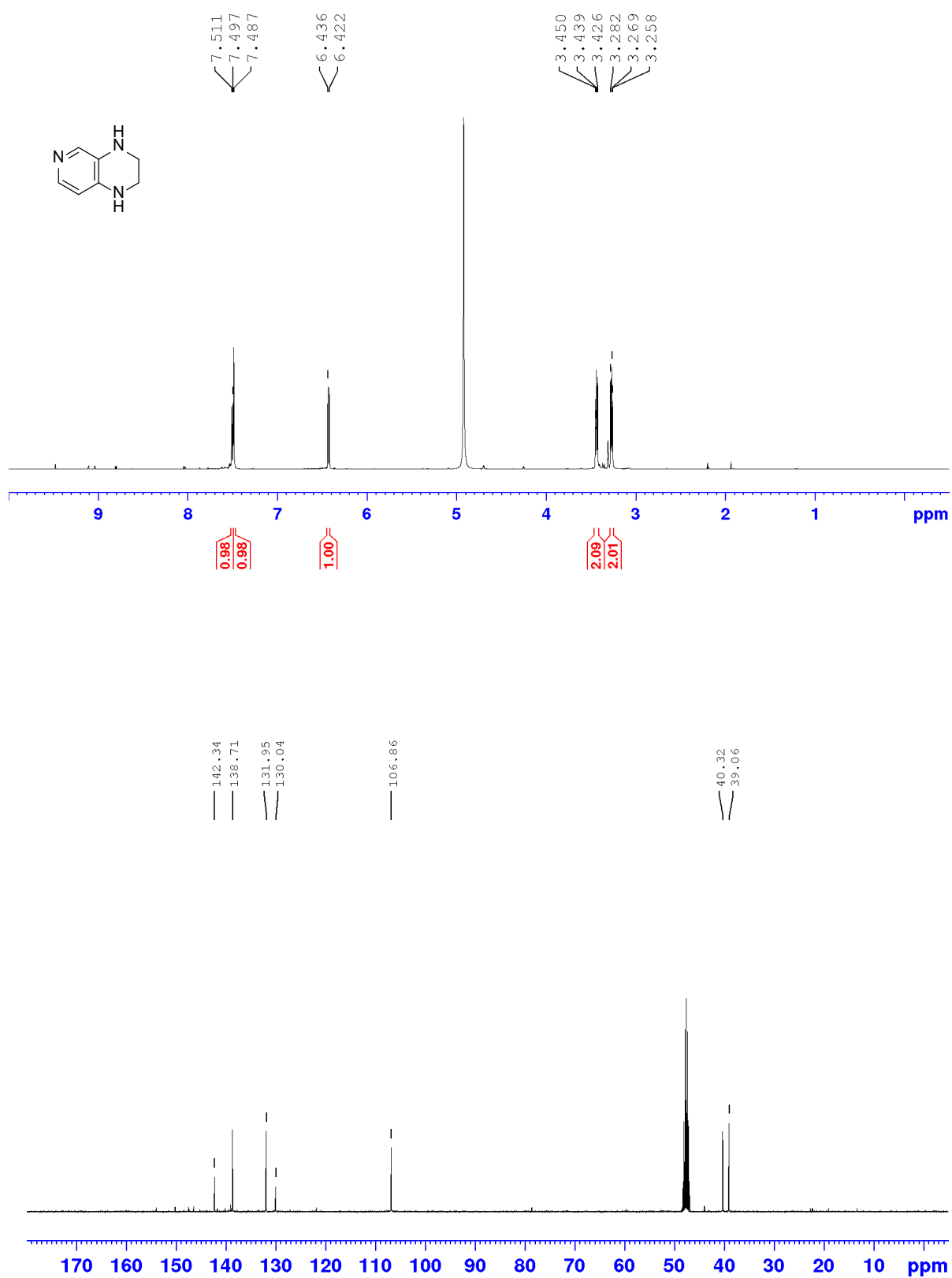
N-(1,2,3,4-tetrahydroquinoxalin-6-yl)acetamide (**27**)



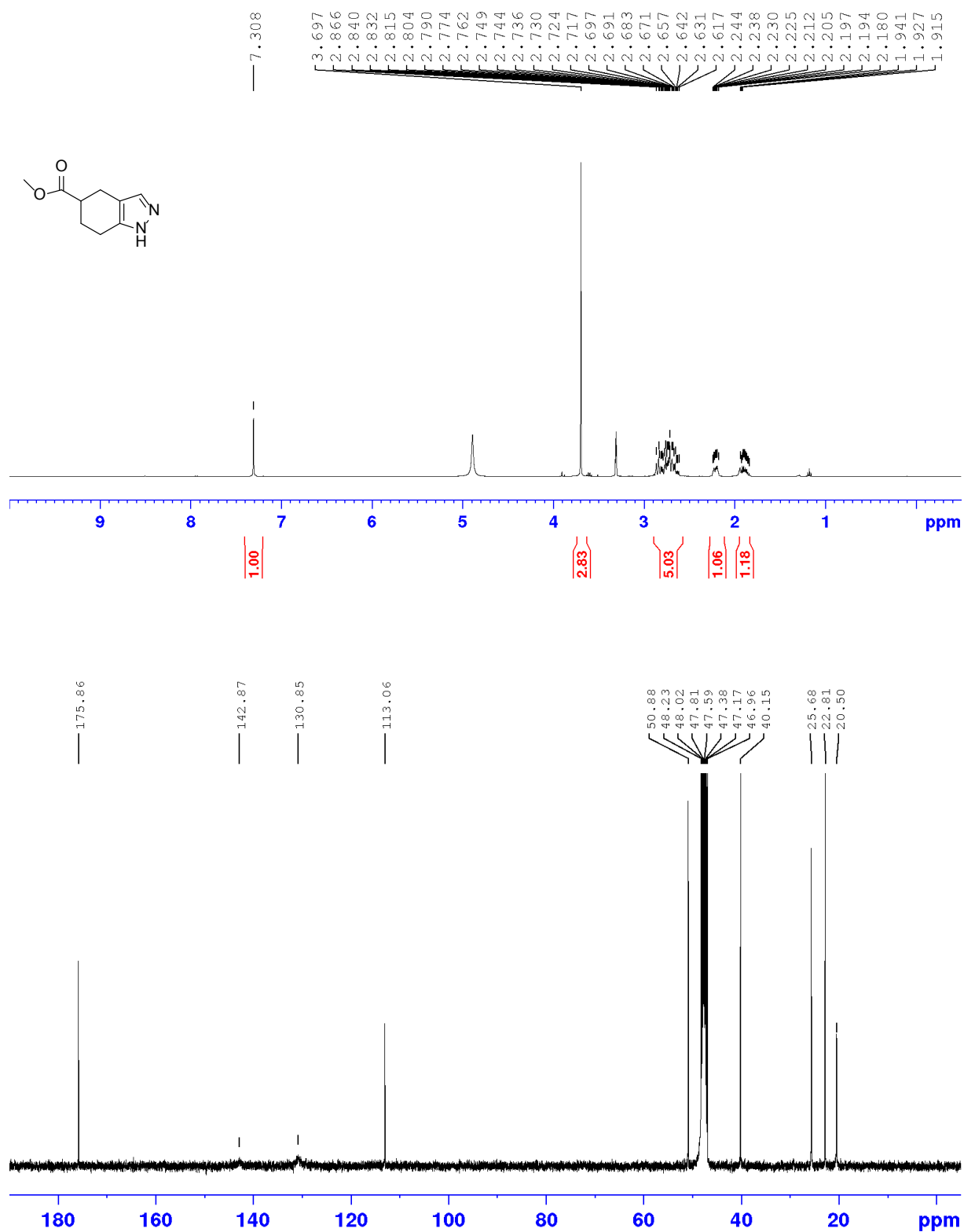
ethyl 5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-2-carboxylate (**28**)<sup>7</sup>



1,2,3,4-tetrahydropyrido[3,4-b]pyrazine (**29**)<sup>8</sup>

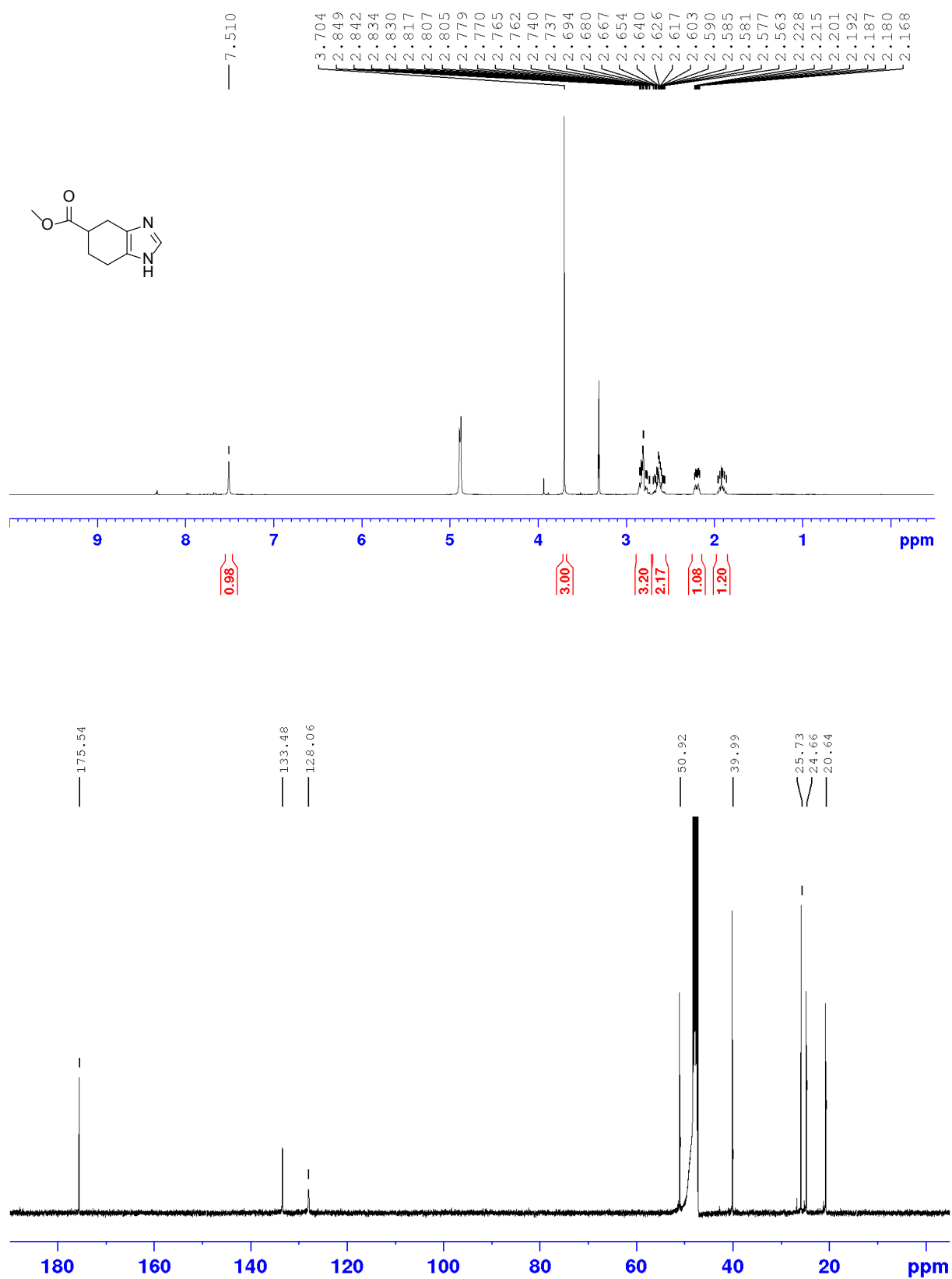


methyl 4,5,6,7-tetrahydro-1H-indazole-5-carboxylate (**30**)<sup>9</sup>

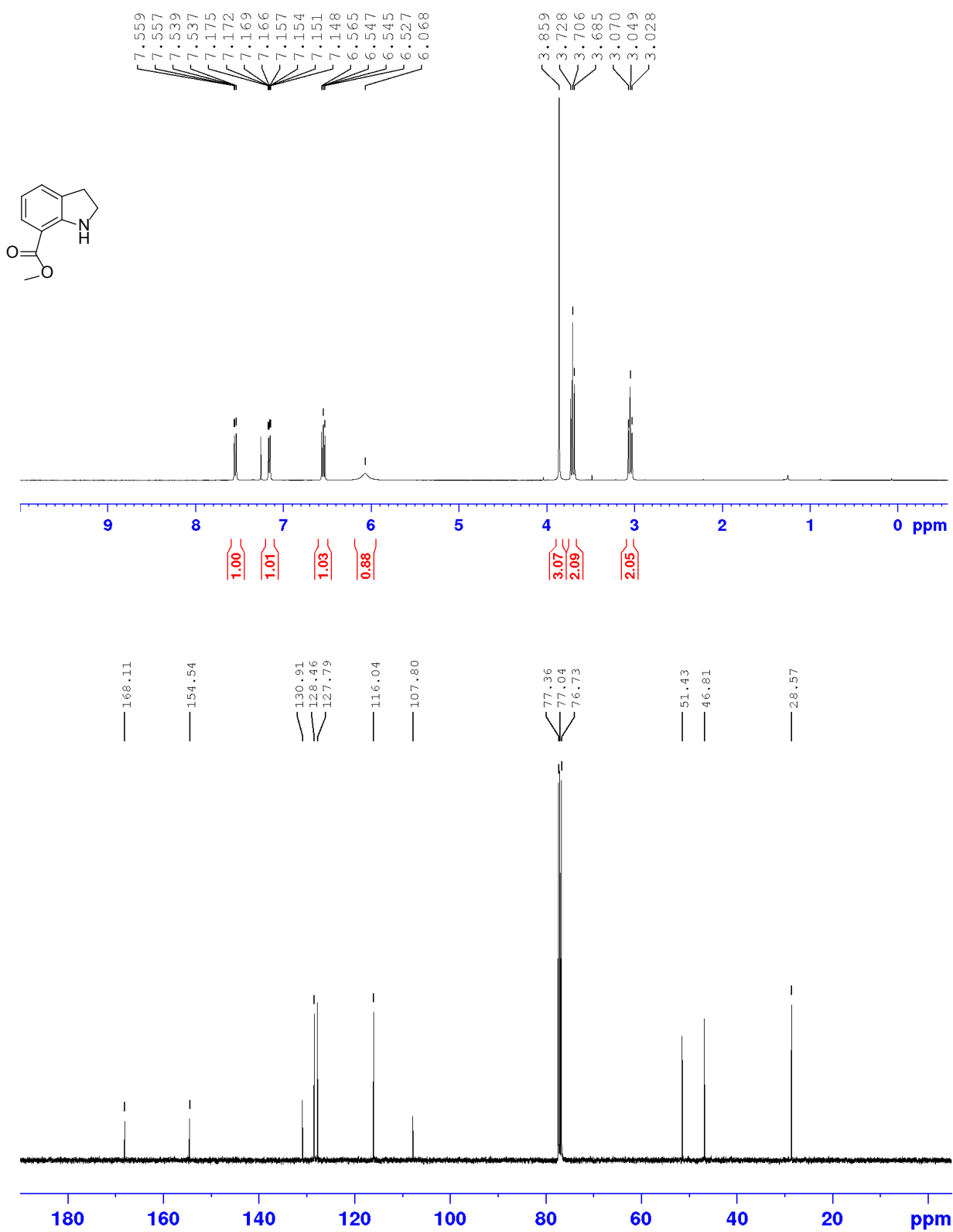




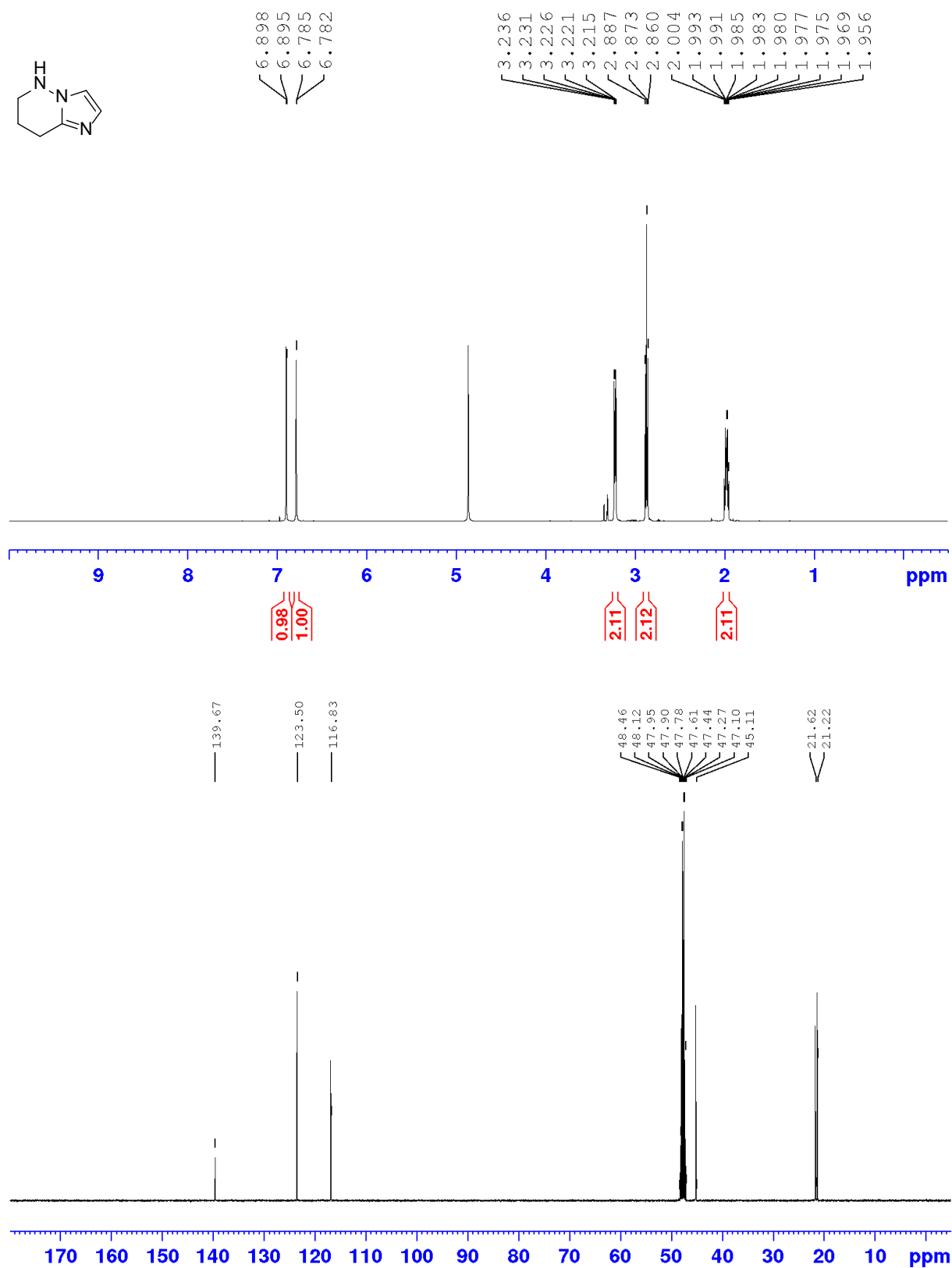
methyl 4,5,6,7-tetrahydro-1H-benzo[d]imidazole-5-carboxylate (**31**)<sup>10</sup>



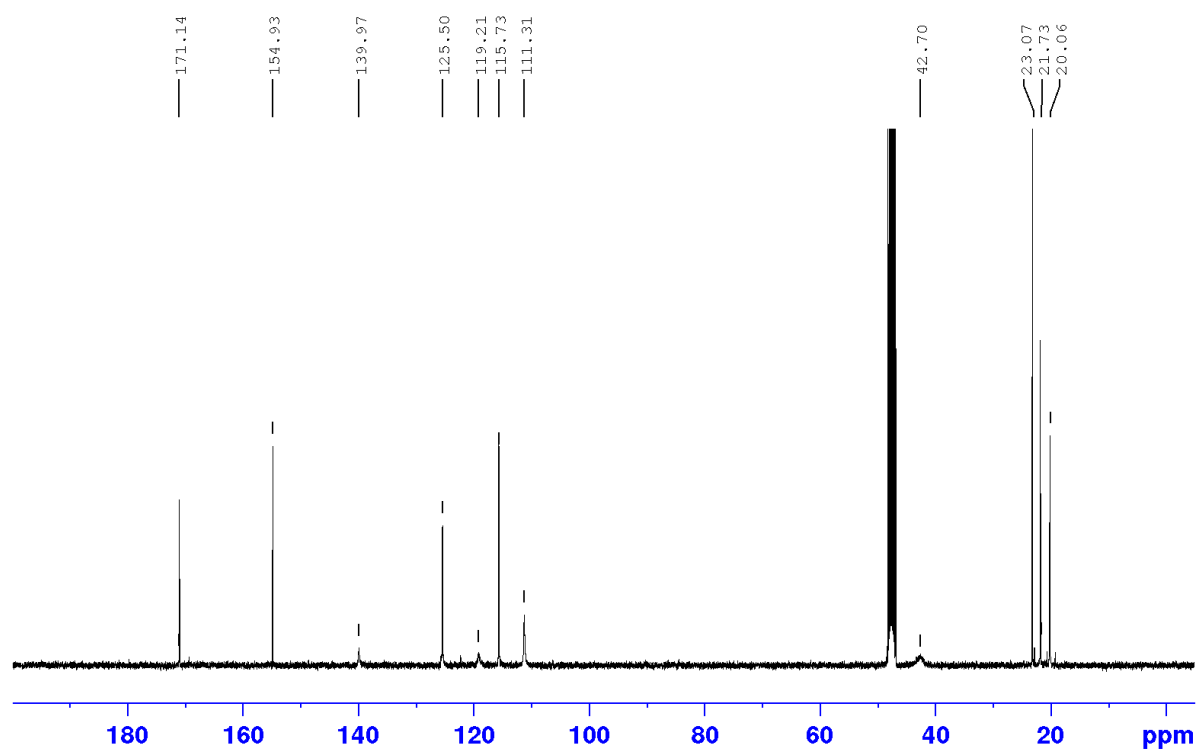
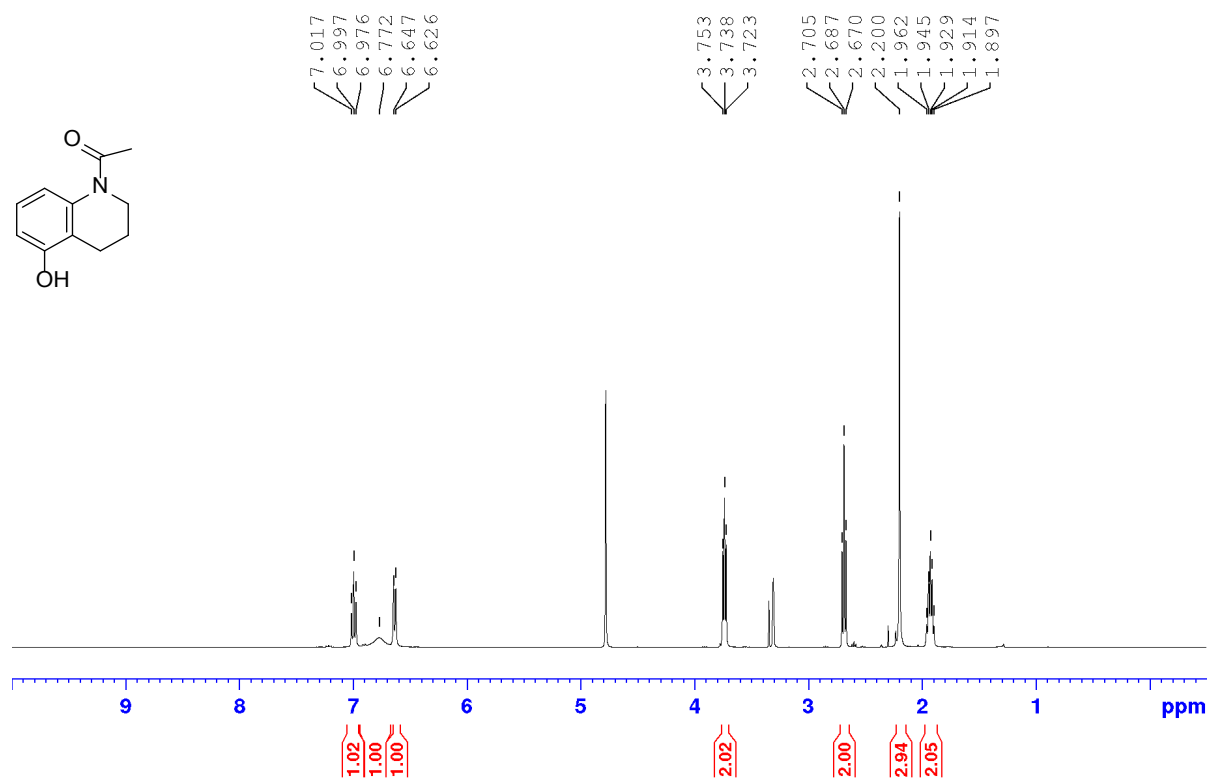
methyl indoline-7-carboxylate (**32**)<sup>11</sup>



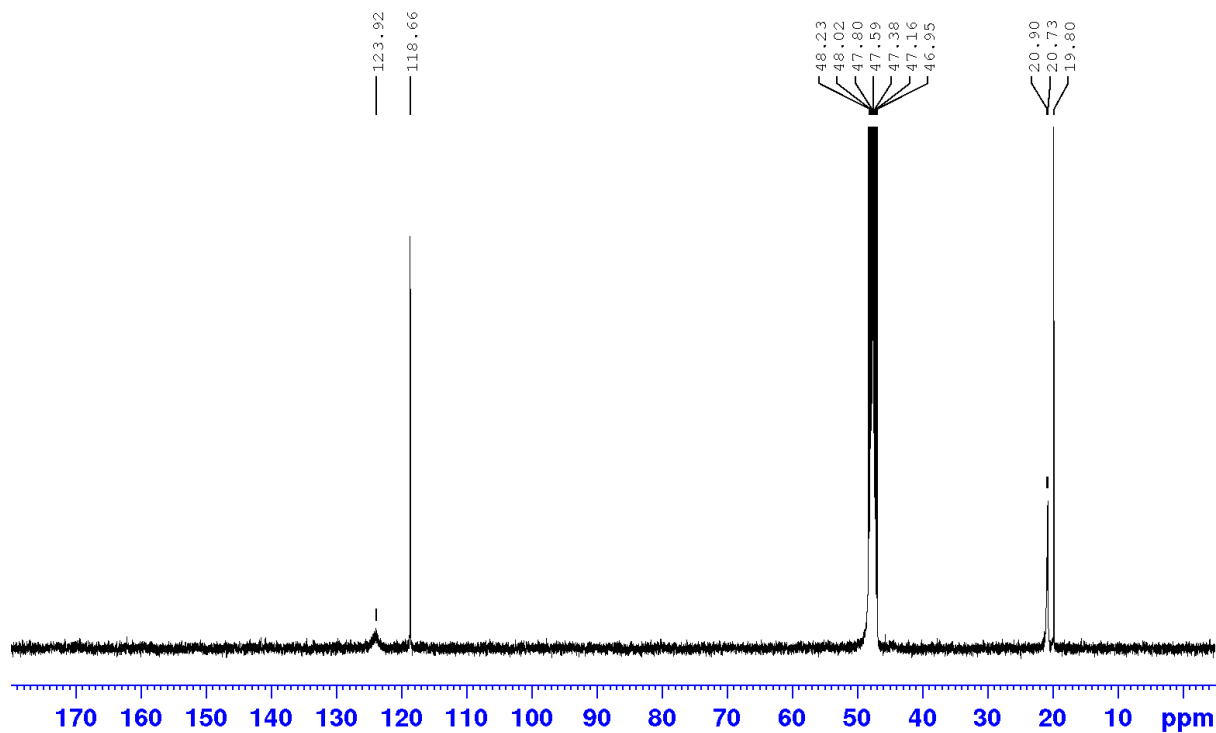
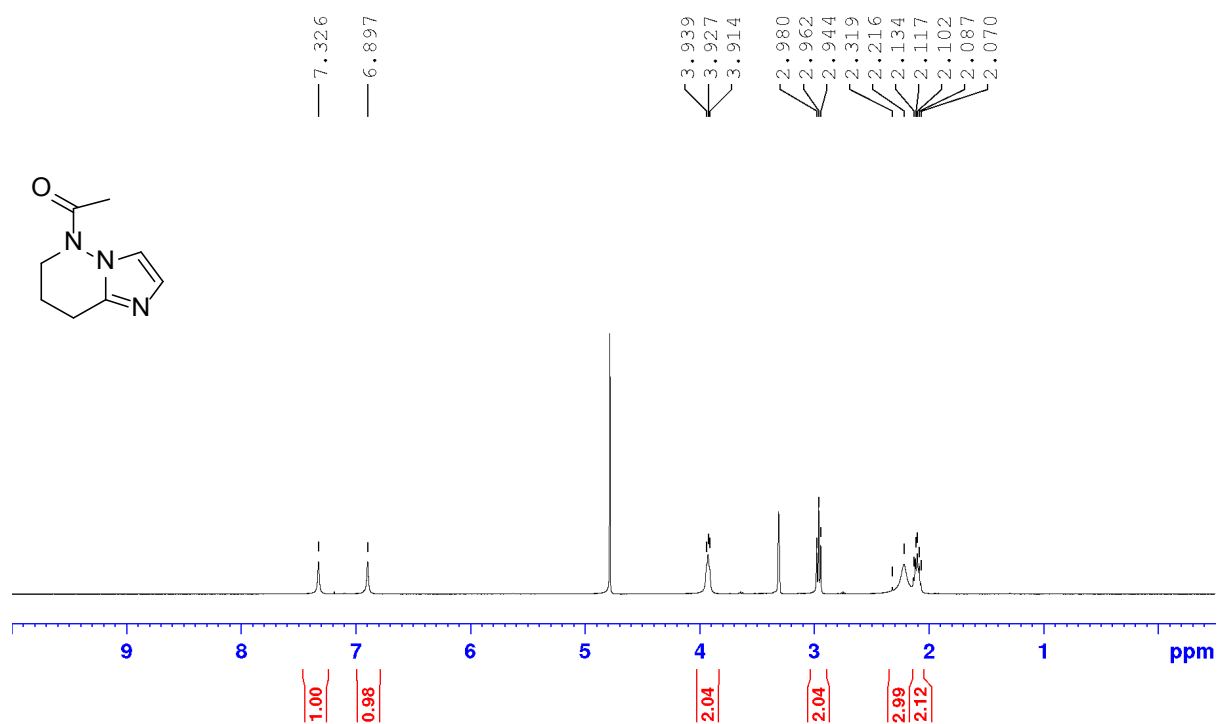
5,6,7,8-tetrahydroimidazo[1,2-b]pyridazine (**33**)<sup>12</sup>



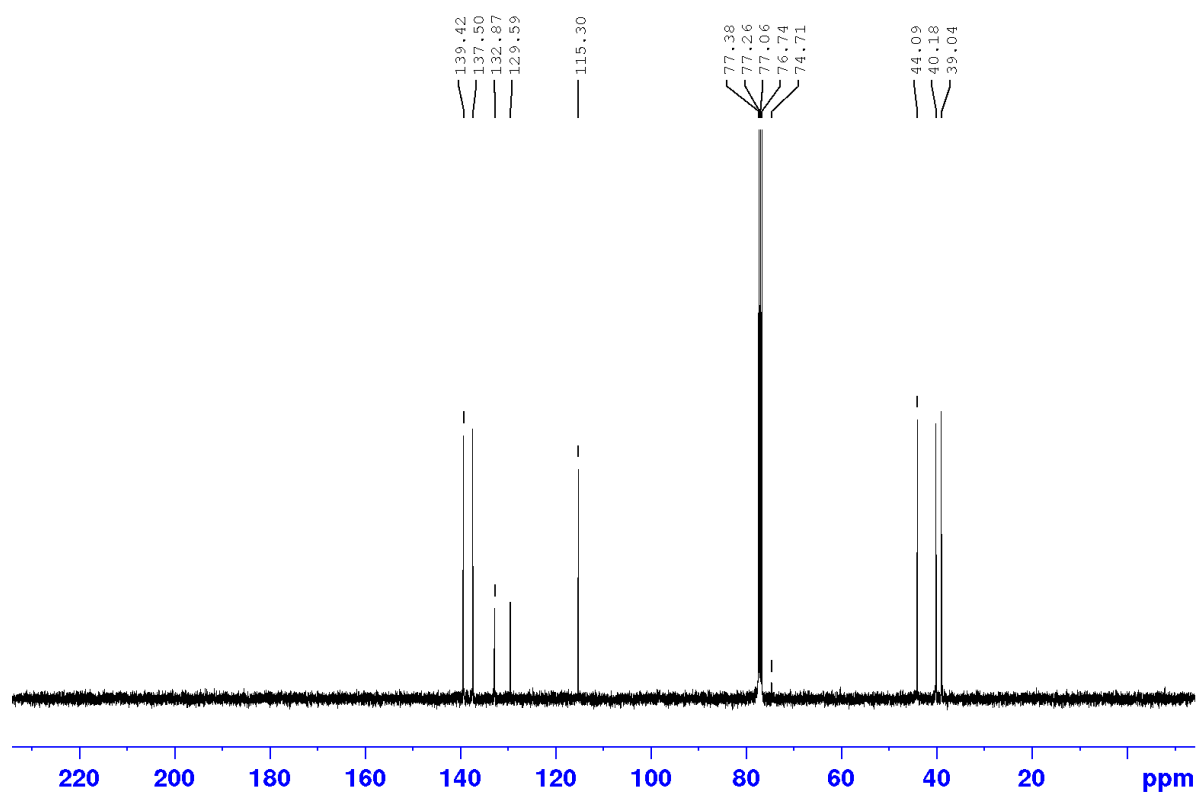
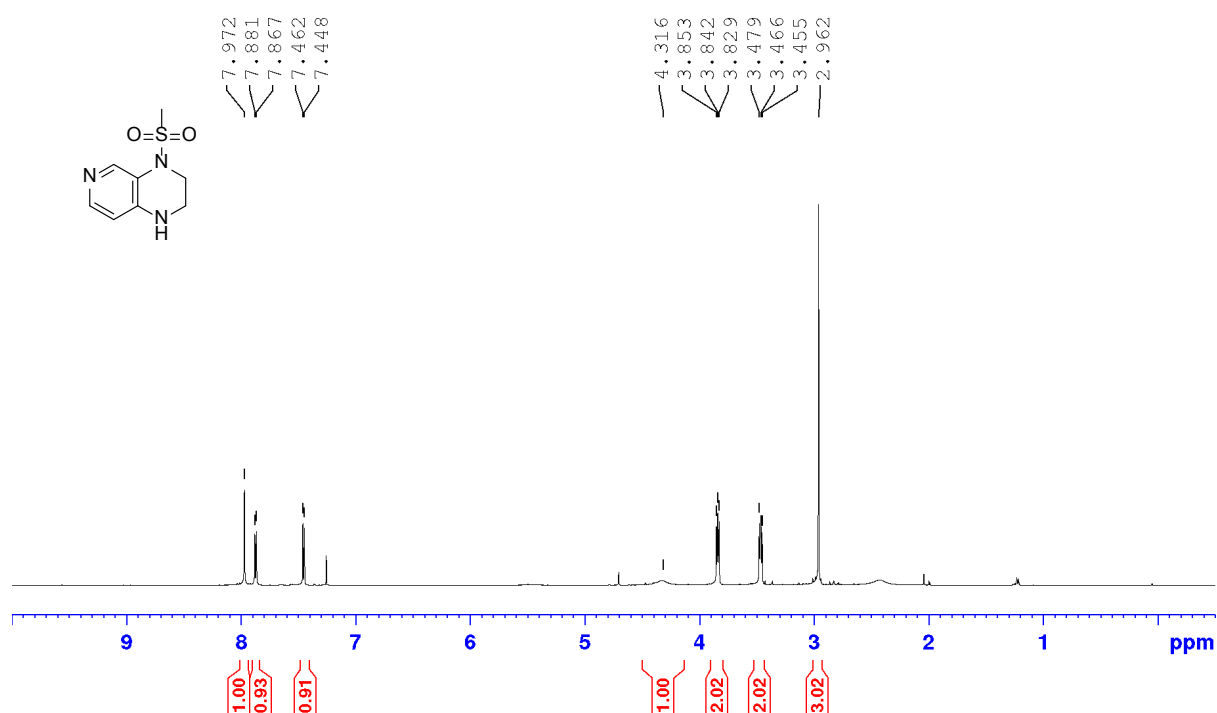
1-(5-hydroxy-3,4-dihydroquinolin-1(2H)-yl)ethan-1-one (**35**)



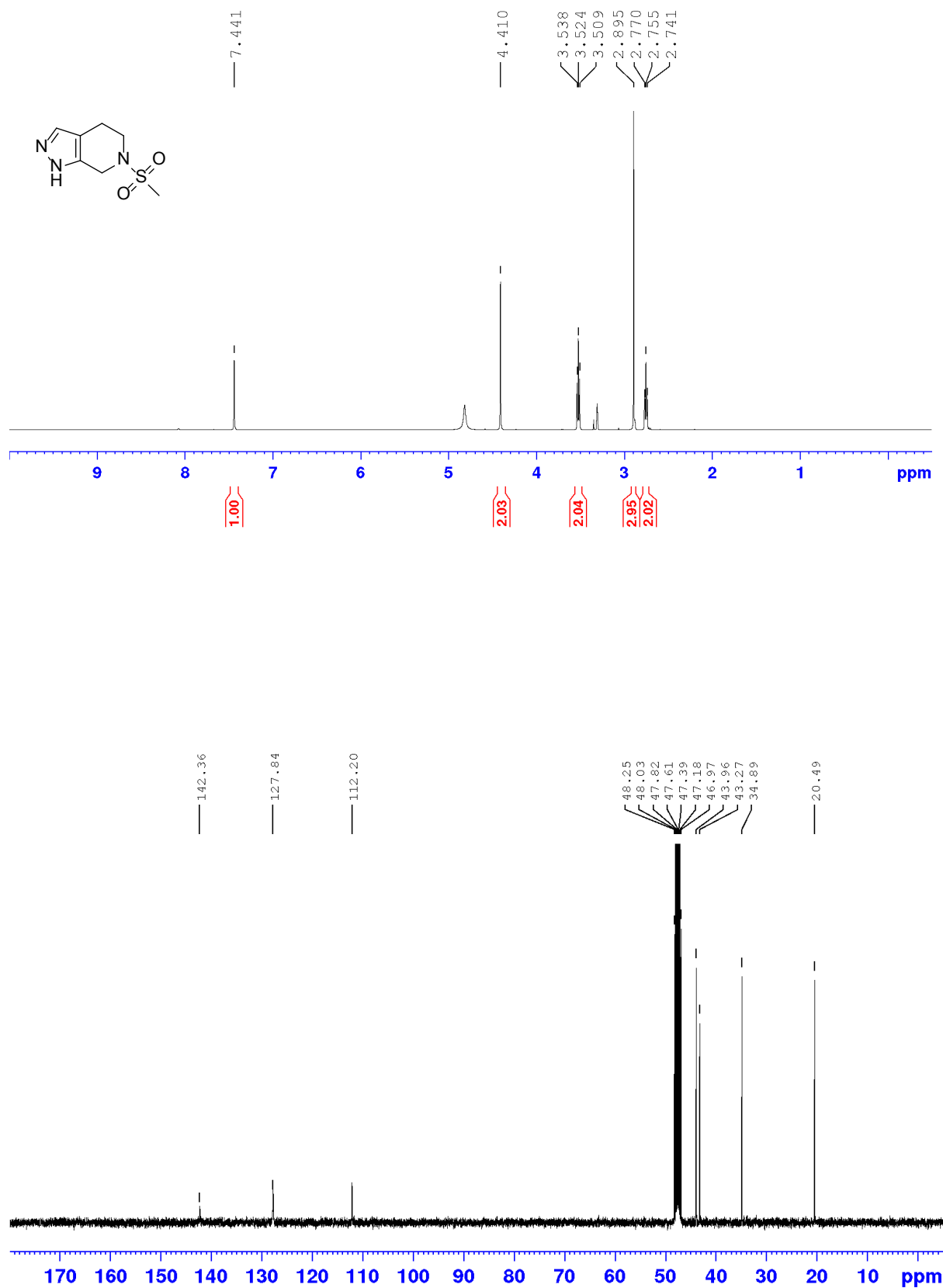
1-(7,8-dihydroimidazo[1,2-b]pyridazin-5(6H)-yl)ethan-1-one (**36**)



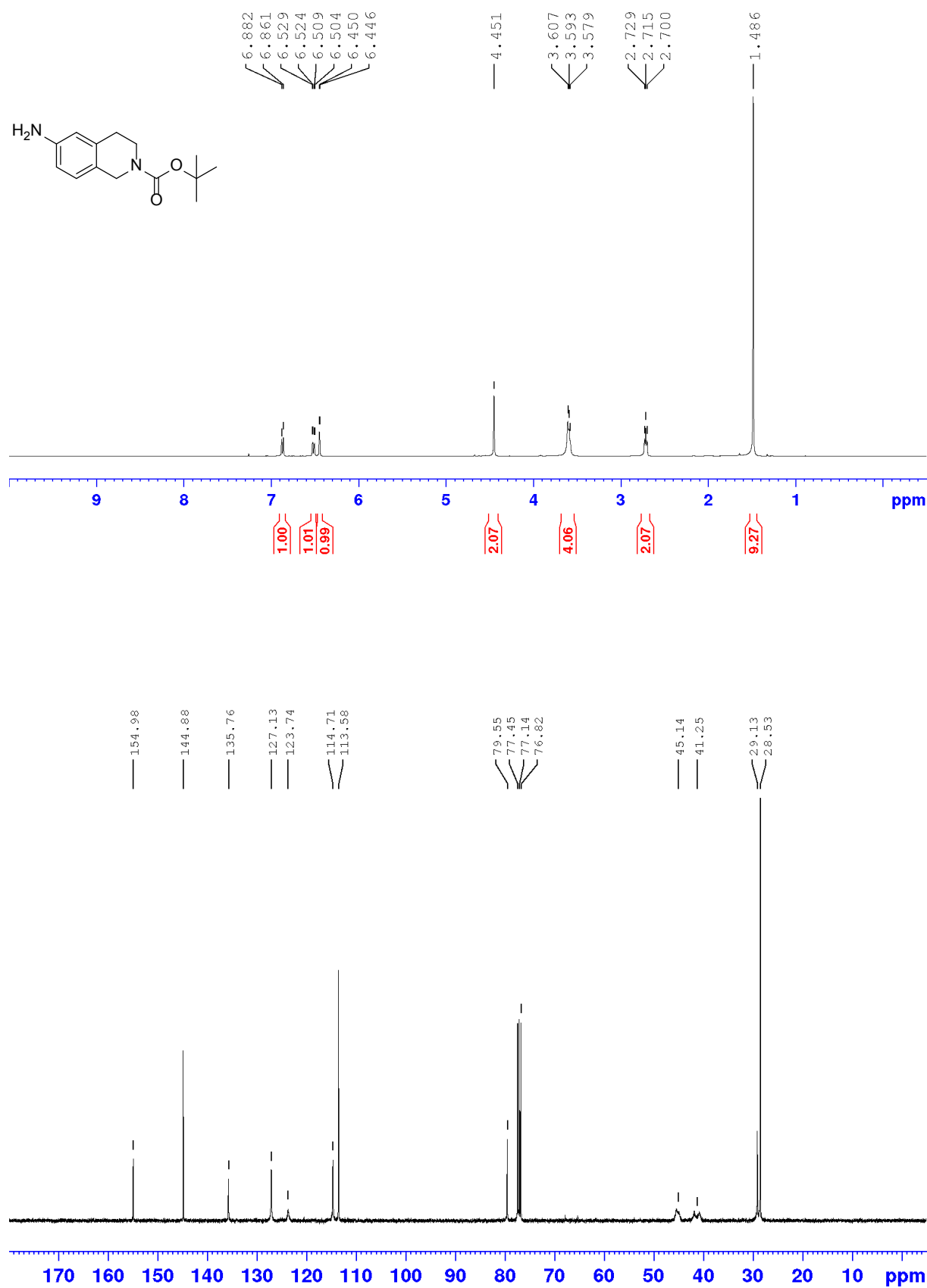
1-(methylsulfonyl)-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine (**37**)



6-(methylsulfonyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine (**38**)

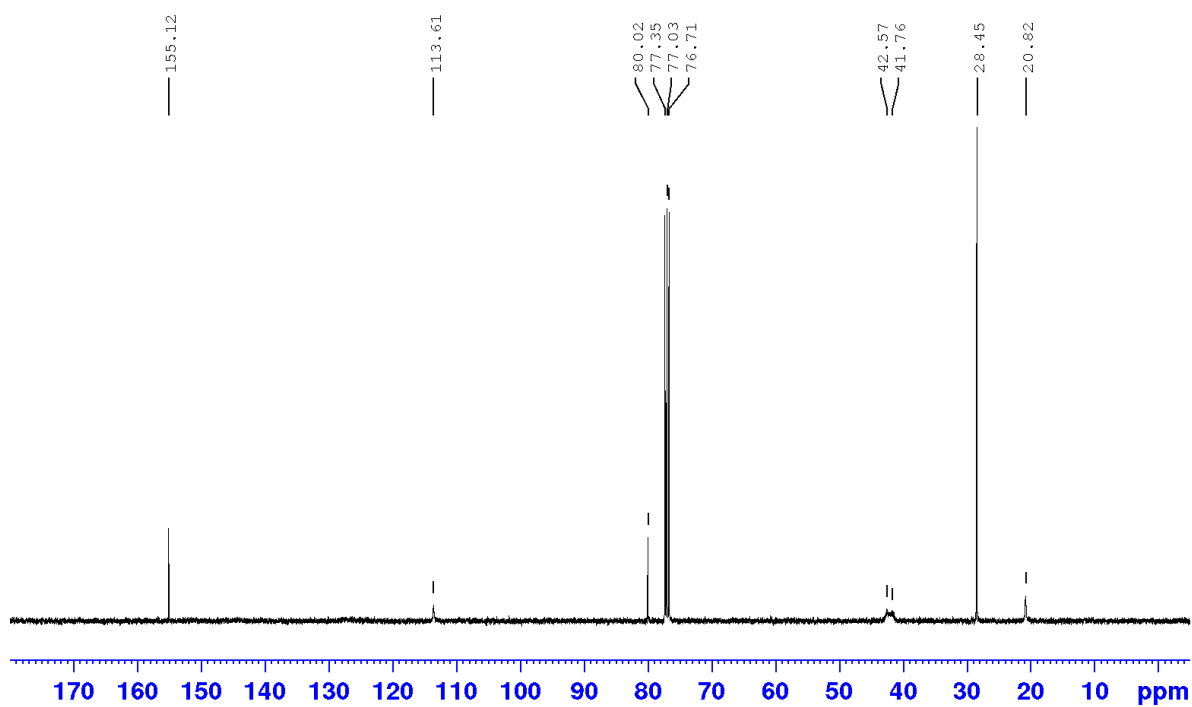
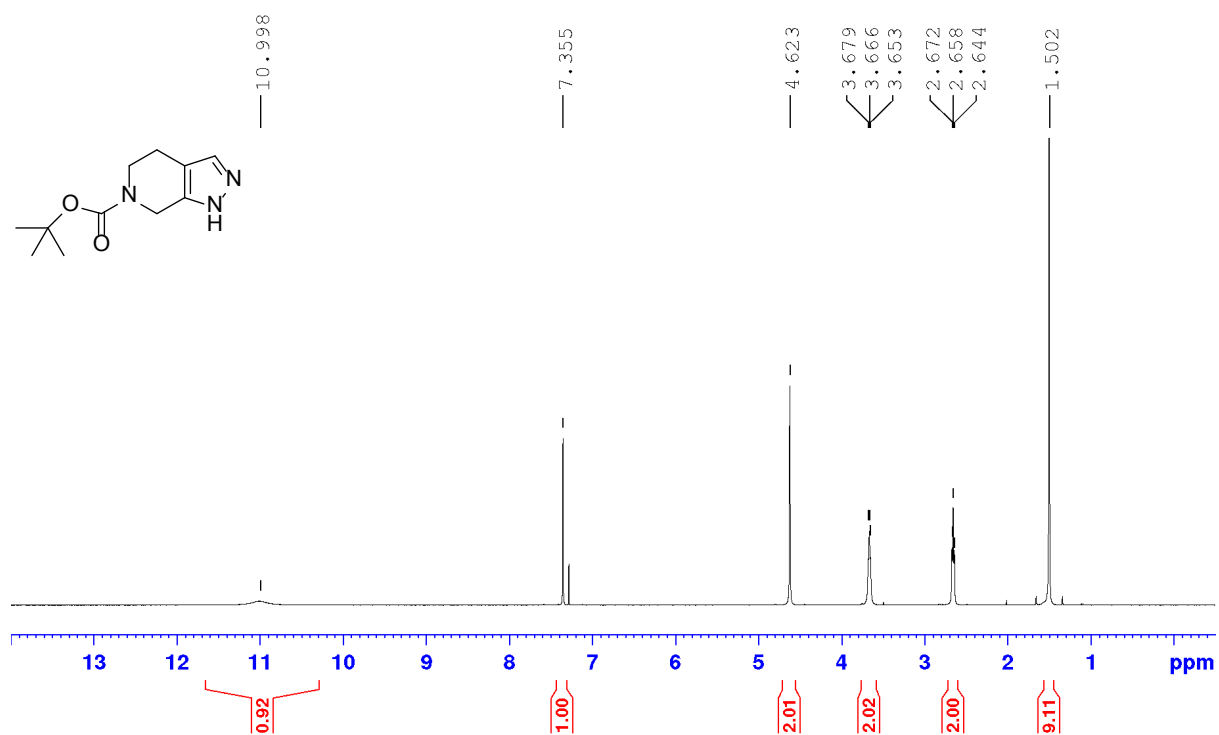


tert-butyl 6-amino-3,4-dihydroisoquinoline-2(1H)-carboxylate (**39**)<sup>13</sup>

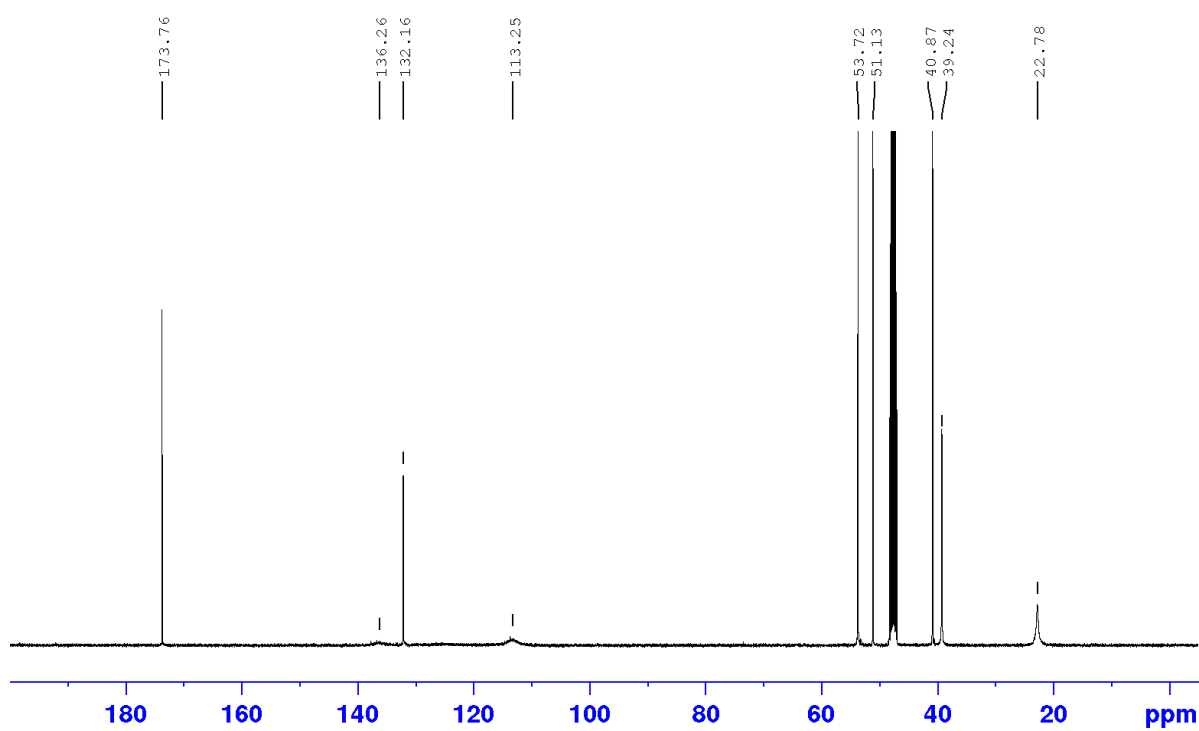
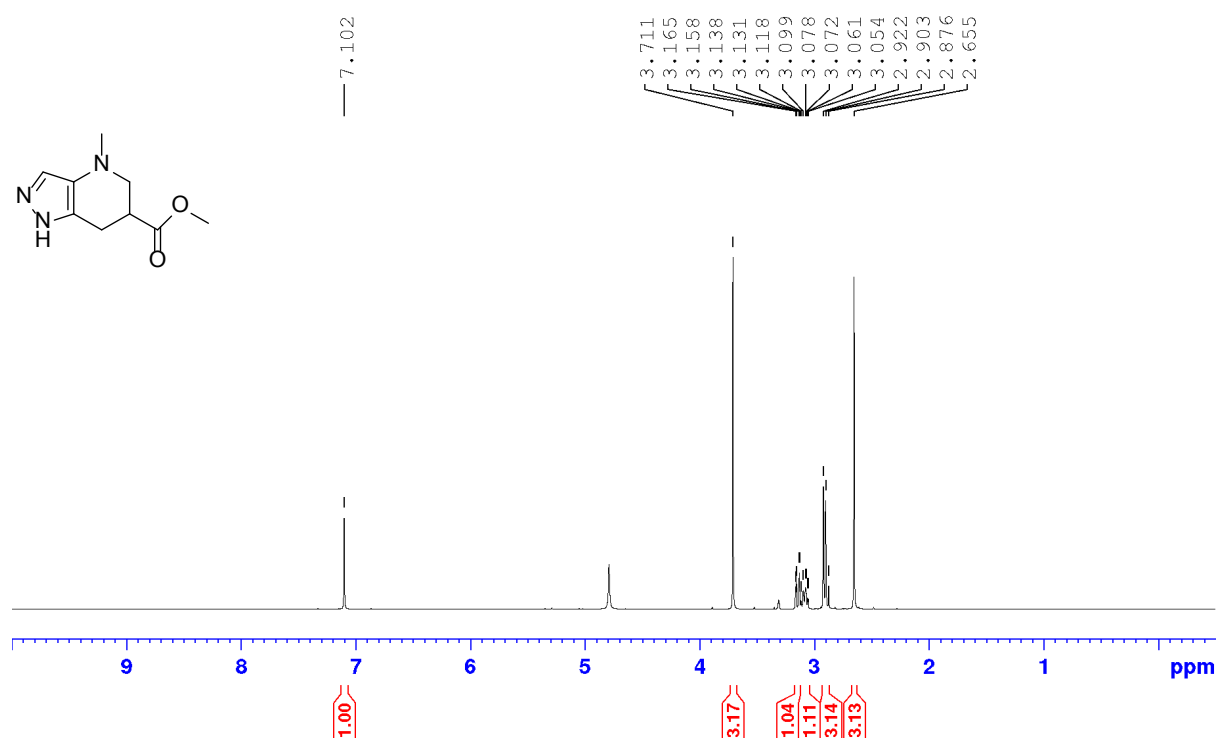




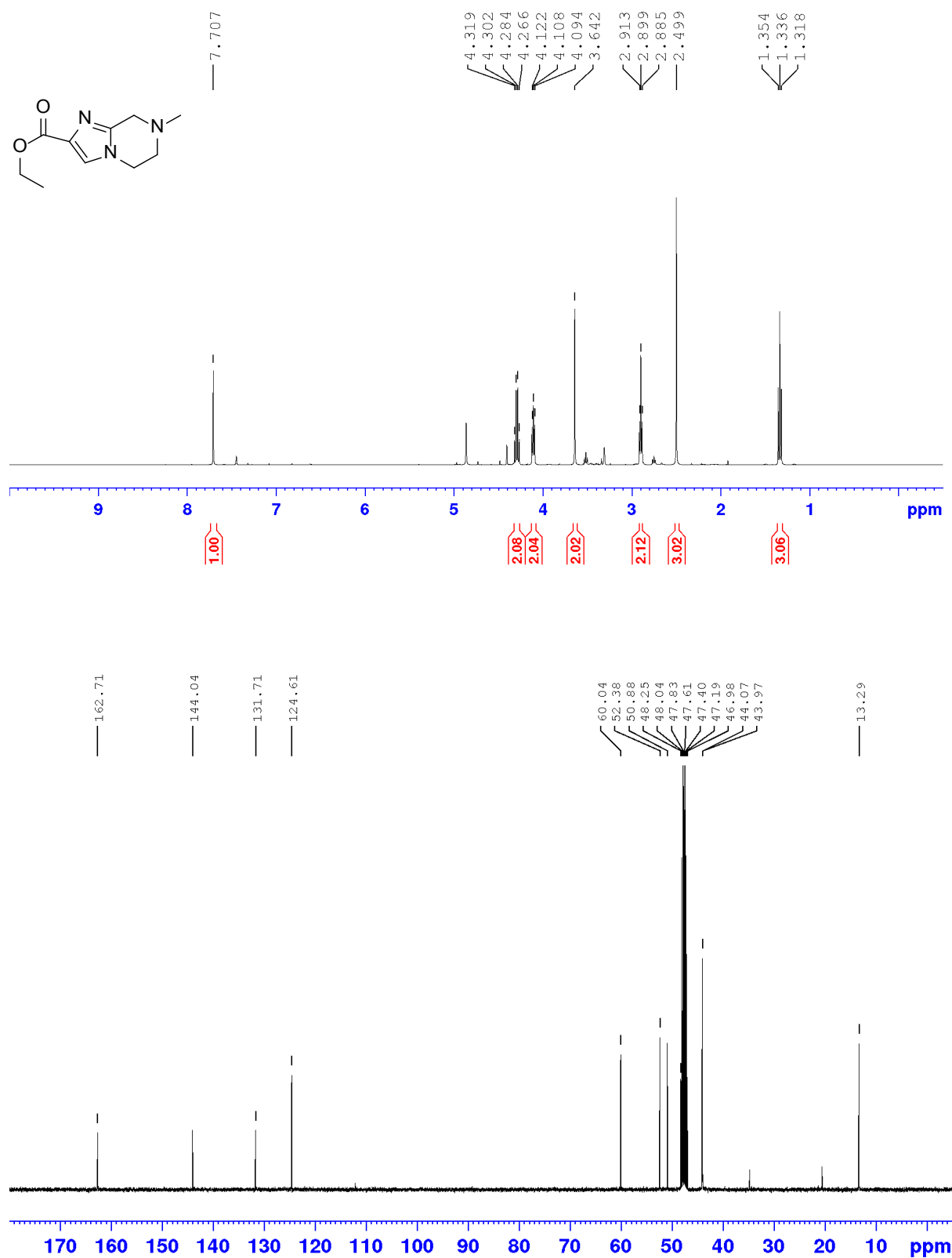
tert-butyl 1,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridine-6-carboxylate (**40**)<sup>14</sup>



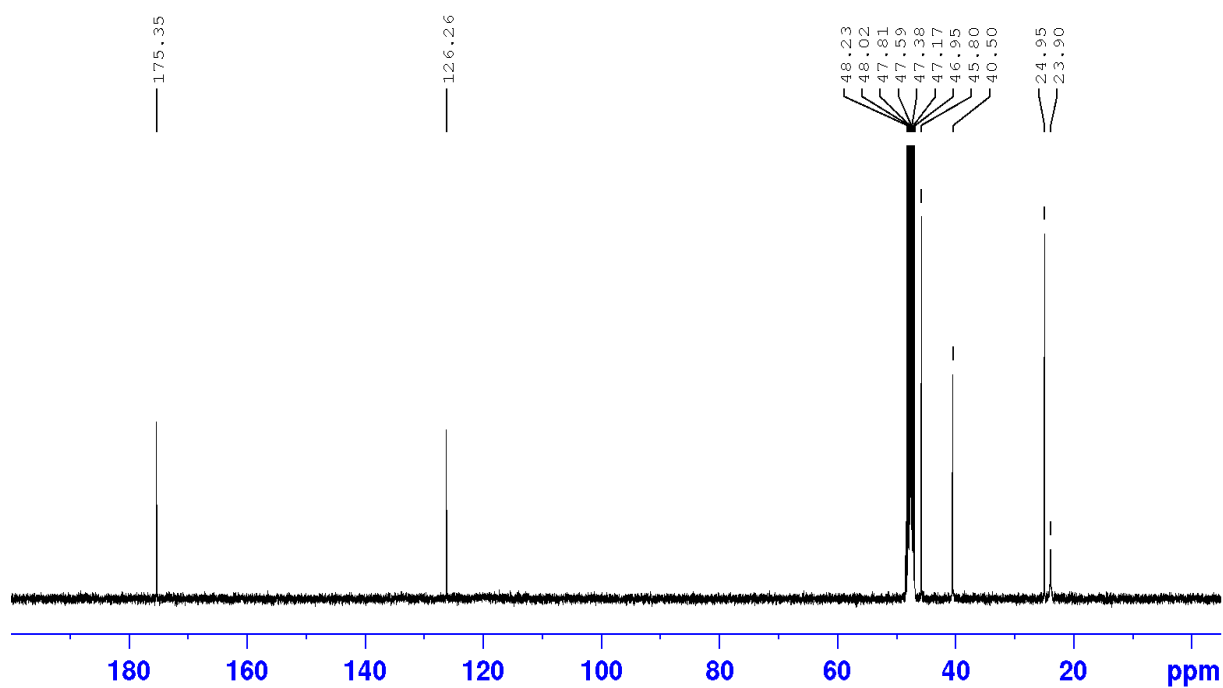
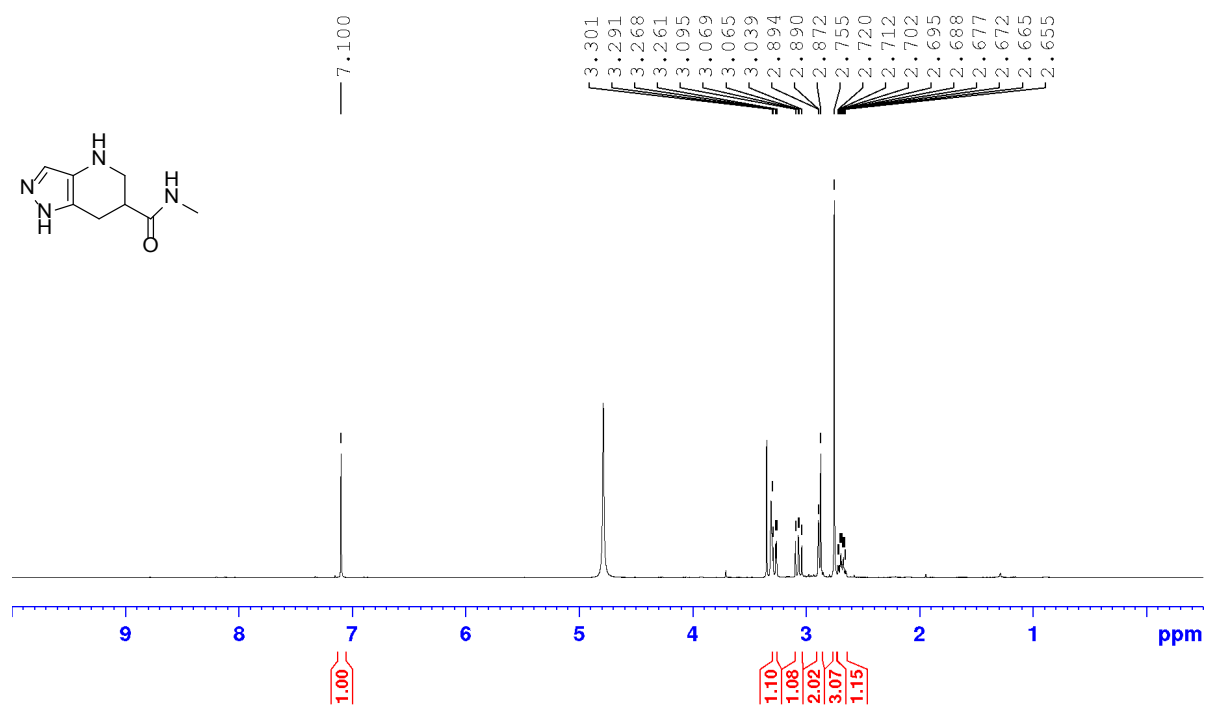
methyl 4-methyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-b]pyridine-6-carboxylate (**41**)



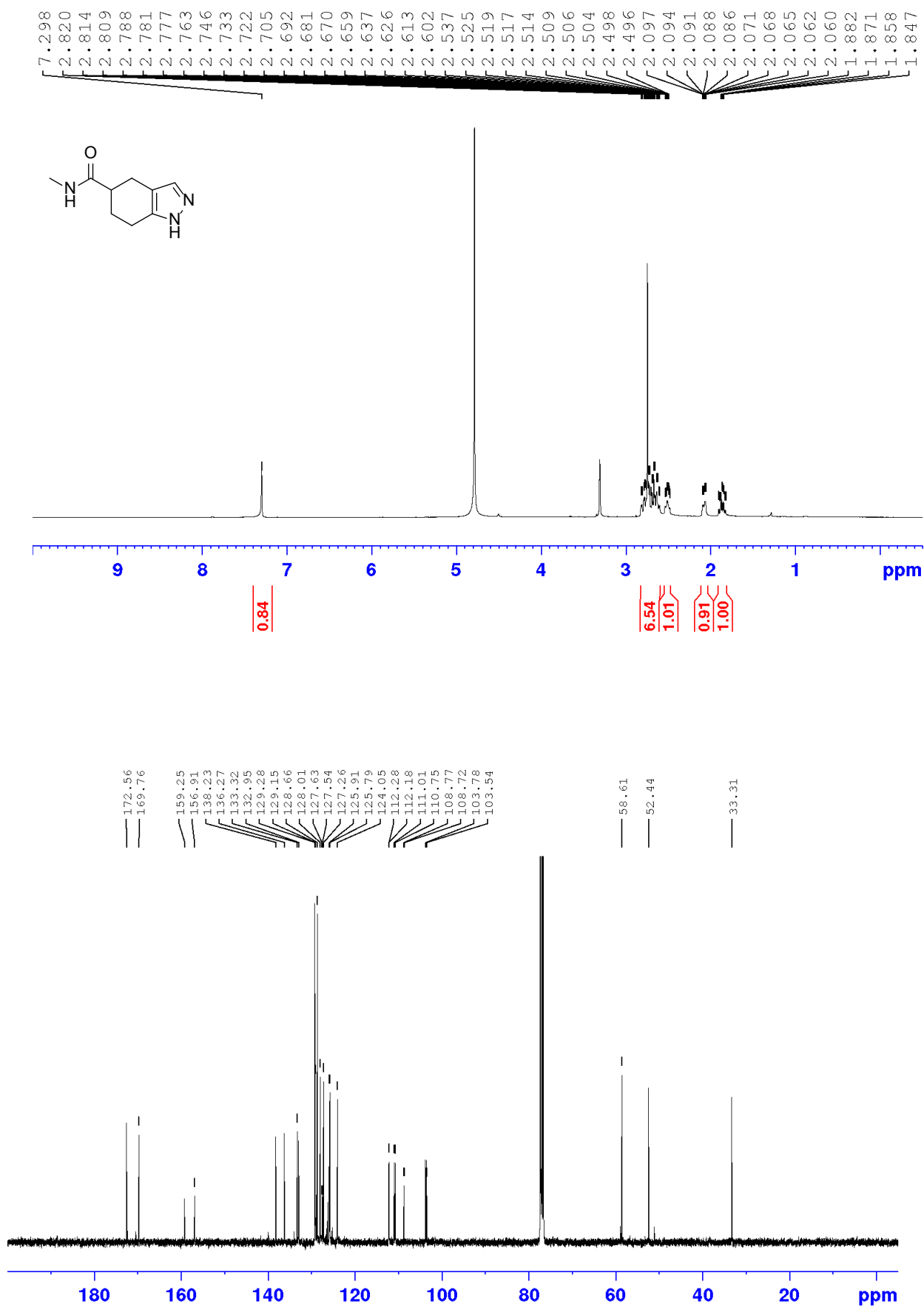
ethyl 7-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-2-carboxylate (**42**)<sup>15</sup>



N-methyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-b]pyridine-6-carboxamide (**43**)



N-methyl-4,5,6,7-tetrahydro-1H-indazole-5-carboxamide (**44**)



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